Appendix E Evidence tables

Review Question 1: Pharmacological management

Table 37 Evidence table for Perlin et al (1994)

Bibliographic reference (Ref ID)	Perlin et al 1994 (Ref ID: 2168)
Study type & aim	Randomised Controlled Trial (RCT)/ To evaluate the IV infusional use of Ketorolac in a double blind, placebo-controlled study
Number and characteristics of patients	Total: 21 patients enrolled (10 in intervention, 11 in placebo). 1 patient in the intervention and 2 patients in placebo group were withdrawn prematurely. Exclusions: Patients under 15 years old, those with active peptic ulcer disease, systemic bleeding disorders, impaired renal function or other medical condition likely to complicate their participation in the study, those with hypersensitivity to NSAIDs and pregnant women. Inclusion: Patients with electrophoretically proven sickle cell disease who were experiencing moderate to severe pain as a result of an acute vaso-occlusive crisis. All patients were ketorolac naive. Patient characteristics: Patients in the intervention group were significantly younger (mean 24 vs. 32 years) and lighter (mean 132lbs vs. 149lbs) compared to patients in the placebo group. No significant differences were found with any other characteristics (this included sex). There were no significant differences between the average number of admissions and average duration of hospital stay in 1990 and 1991 therefore it was believed that the difference in mean age between groups would have little impact on outcomes. One patient in the Ketorolac treated group had SC genotype and one had S/Th; the remainder had SS. One patient in the placebo group had S/Th and the remainder had SS.
Monitoring information and definitions	Pre-study: All patients had been admitted to hospital before enrolment and had received routine treatment which included intramuscular injections of meperidine and oral hydroxyzine pamoate in addition to adequate oral and/or IV hydration. Pain scale: Verbal Categoric Scale (VCS) 0=no pain, 1=mild, 2=moderate, 3=severe pain, a 100mm Visual Analogue Scale (VAS) where 0=no pain and 100= worst pain possible and a Pain Relief Verbal Scale where 0=none, 1=a little, 2=some, 3=a lot and 4=complete. At the end of the study a global assessment was obtained by asking patients to compare the analgesic regimen just received with that received for previous sickle cell crises where 1=much worse, 2=worse, 3=same, 4=better and 5=much better. Monitoring: Pain intensity over the preceding 24 hours was assessed daily, at approximately the same time each morning Duration of hospital stay: measured the day of enrolment in the study to the day of discharge

<table>
<tr><td>Intervention</td><td>Drug: Ketorolac (diluted in D_5 in ½ normal saline).
Dose and timing: Loading dose of 30mg over the first 40 minutes, thereafter patients received an infusion of 120mg at 5mg/hr for a total dose of 150mg on the first day. For the remainder of the study, patients received 120mg/day.
Route: Peripheral intravenous line (central IV lines were not used)
Other pain relief: Meperidine 100mg IM was administered every 3 hours if patients reported moderate pain to the staff nurse and requested relief.
Duration of treatment: 5 days. Patients who continued to require analgesia beyond the 5 days of infusion received IM meperidine and oral hydroxyzine</td></tr>
<tr><td>Comparator</td><td>Drug: Normal saline (placebo).
Dose and timing: Infusion received at same rate as ml/hr rate as intervention group.
Route: Peripheral intravenous line.
Other pain relief: Meperidine 100mg IM was administered every 3 hours if patients reported moderate pain to the staff nurse and requested relief.</td></tr>
<tr><td>Length of follow up</td><td>5 days</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Use of meperidine (additional analgesia):
<table>
<tr><td></td><td colspan="2">Treatment group</td></tr>
<tr><td></td><td>Ketorolac</td><td>Placebo</td></tr>
<tr><td>No patients</td><td>9</td><td>11</td></tr>
<tr><td>Mean total dose required mg (±SD)</td><td>1866.7 (1112.4)</td><td>2804.5* (795.1)</td></tr>
<tr><td>Mean daily dose mg (±SD)</td><td>523.6 (222.1)</td><td>662.4 (68.6)</td></tr>
</table>
*Significant difference between groups showing a 33% (938mg) reduction in ketorolac group compared to placebo, p=0.04
Quality of analgesia (pain intensity):
<table>
<tr><td></td><td>Ketorolac</td><td>Placebo</td></tr>
<tr><td colspan="3">No patients</td></tr>
<tr><td colspan="3">Mean pain intensity (VCS) 0-3</td></tr>
<tr><td>Baseline</td><td>2.5</td><td>2.6</td></tr>
<tr><td>Day 1</td><td>2.0</td><td>2.4</td></tr>
<tr><td>Day 2</td><td>1.3</td><td>2.1*</td></tr>
<tr><td>Day 3</td><td>1.1</td><td>1.8*</td></tr>
</table></td></tr>
</table>

Day 4`	1.0	1.7*
Day 5	1.1	1.7*
Mean pain intensity (VAS) 0-100mm (95% CI)		
Baseline	77.7 (69.1-86.2)	79.1 (72.1-86.0)
Day 1	58.6 (48.6-68.5)	72.6 (62.4-82.8)*
Day 2	48.7 (33.0-64.4)	64.6 (53.7-75.6)
Day 3	37.0 (16.3-57.7)	60.8 (49.2-72.4)*
Day 4	32.0 (12.7-51.3)	54.7 (41.8-67.6)*
Day 5	32.4 (11.7-53.2)	52.9 (38.0-67.8)
Mean pain relief score (verbal scale) 0-4		
Day 1	1.8	1.9
Day 2	2.1	1.9
Day 3	2.8	2.0*
Day 4	2.8	2.3
Day 5	2.7	2.4
Comparison with previous treatment (global assessment) 1-5		
Mean score	4.0	3.3*

*Significant difference between ketorolac and placebo group ($p<0.05$).

The table of quality of analgesia shows that after day 1, all the differences in mean VCS scores are statistically different. Similarly, the differences between the two groups with respect to VAS were statistically significant on days 1, 3 and 4. Mean scores for pain relief assessments are also shown in the table above. Only two patients reported complete relief of pain, by the end of the third day, and both were in the Ketorolac group. Although the mean scores for pain relief every day after the first day were higher in the Ketorolac group than in the placebo group, these differences only reached statistical significance on day 3.

Duration of infusions and days in hospital:

	Ketorolac	**Placebo**
No of patients	9	11
Median duration in hospital for infusion (days)	3.0	5.0

Median duration in hospital post-infusion	<1	3.0
Median duration in hospital for study	3.3	7.2*
No of patients requiring infusion		
Day 1	10[a]	11
Day 2	9	11
Day 3	8	10[b]
Day 4	4	9[c]
Day 5	3	8*

*Difference between Ketorolac and placebo significant ($p < 0.05$)
[a] one patient was inappropriately enrolled and was treated for only 1.5 hours
[b] one patient was withdrawn because of lack of analgesia
[c] one patient was withdrawn because of adverse event

Median duration in hospital for study (days) was significantly higher in the placebo group (placebo=7.2 days vs. ketorolac= 3.3, p=0.027). By the end of the scheduled 5-day infusion, six of the Ketorolac patients but only one of the placebo patients had discontinued treatment because it was no longer needed. The time to termination of the infusion was significantly shorter in the Ketorolac group ($p = 0.009$).

Adverse events reported during study stratified by body system*:

	Ketorolac	**Placebo**
Total patients enrolled	10	11
Digestive system:	5	4
Constipation	2	2
Nausea	3	1
Vomiting	2	2
Diarrhoea	2	0
Dyspepsia	2	0
Dysphagia	0	1
Abnormal liver function	0	1
Body as a whole:	3	5
Fever	1	2

	<table><tr><td>Abdominal pain</td><td>1</td><td>1</td></tr><tr><td>Headache</td><td>1</td><td>1</td></tr><tr><td>Chest pain</td><td>0</td><td>2</td></tr></table> *In addition, one patient in Ketorolac group reported epistaxis and one reported pruritus; one placebo patient reported insomnia Most adverse events involved the digestive system. In particular no renal effects were reported. Two patients who received placebo and meperidine developed acute chest syndrome (mapped to chest pain in the table above).
Authors' conclusion	The study showed that continuous infusion of ketorolac significantly reduced total meperidine requirement and that the analgesia produced by this combination was superior to that produced by meperidine alone.
Source of funding	This study was supported in part by a grant from Syntex Research, a division of Syntex (USA) Inc who manufacture ketorolac as Toradol.
Comments	One patient was inappropriately enrolled due to warfarin use (received ketorolac for 1.5 hours and results are only included in safety analysis). 2 patients in the placebo group were withdrawn prematurely (one due to lack of adequate analgesia and one due to liver disease). The study drugs were prepared by a designated hospital pharmacist and allocated according to a pre-determined; computer generated random code, balanced in blocks of four. When data relating to quality of analgesia from a particular patient was not available, the last valid measurement or evaluation was carried forward in an attempt to minimise the bias inherent in basing comparisons solely on those patients remaining in the study at a given time.

Table 38 Evidence table for Wright et al (1992)

Bibliographic reference (Ref ID)	Wright et al 1992 (Ref ID: 2333)
Study type & aim	Prospective, randomised, single-dose, double blind study/ To determine if a single dose of intramuscular ketorolac given on presentation to the emergency department has a narcotic-sparing effect in adult patients with sickle cell vaso-occlusive crisis pain.
Number and characteristics of patients	Total: 18 patients enrolled (6 patients were enrolled twice for a total of 24 patient visits in the study-12 in each group). 2 other patients were allergic to the study medications and were not enrolled and 2 refused to participate. Exclusions: Patients with an allergy to one of the study drugs, those with a history of active peptic ulcer disease, bleeding disorders or use of analgesics or central nervous system active drugs during the three hour period before administration of the study medication. Patients with known or suspected acute complication of sickle cell anaemia were also excluded. Inclusions: Adult patients with sickle cell anaemia who present to the Emergency Department (ED) at either Vanderbilt University Hospital or Metropolitan Nashville General Hospital with a chief complaint of crisis. Patients were enrolled on a convenience basis over a ten-month period. Only patients who rated their pain as 'moderate' or 'severe' in intensity were included. Patients could be enrolled twice as long as the ED visits were separated by at least six months. Patient characteristics: Baseline pain score were slightly lower in the ketorolac group but this was not significantly different (p = 0.26). There were a

	significantly higher number of females in the ketorolac group (10 vs. 5, p = 0.045). There was no significant differences in terms of age (ketorolac = 29.8, placebo = 31.9, p = 0.50) and baseline pain category (p = 0.67).
Monitoring information and definitions	Monitoring: Vital signs were taken at the start of the study and at least every 60 minutes. Pre-Study: IV access was obtained on all patients and $D_5$1/2 normal saline was started at 200 ml/hr. Laboratory studies and radiographs were obtained as thought to be indicated by the treating physician. Patients were placed on oxygen at 2 L/min by nasal cannula. The study medication was then administered. Pain scales: pain intensity was measured on both a categorical and 100 mm visual analogue scale at baseline and every 30 minutes for throughout the four hour observation period. Total relief of pain score: baseline VAS score minus the pain score at 240 minutes.
Intervention	Drug: Ketorolac Dose: 60 mg Route: IM Procedure: Patients were randomly assigned to receive either ketorolac or saline placebo. Patients were given further IV doses of meperidine every 30 minutes during the study period as needed based on their pain intensity as rated on the categorical scale. Patients with 'mild' or 'moderate' pain were given meperidine 25 mg and those with 'severe' pain were given meperidine 50 mg. Patients without pain were not given further doses of meperidine unless pain recurred. Timing: no further details reported Other pain relief: All patients were administered meperidine 50 mg IV and promethazine 12.5 mg IV simultaneously with the study medication (patients were administered this initial dose of meperidine at the start of the study because the peak effects of ketorolac may be delayed for up to 1 hour). Other analgesics and sedatives were not administered during the study period.
Comparator	Drug: Saline Dose: Not specifically reported Route: IM Procedure: as above Timing: as above Other pain relief: as above
Length of follow up	Four hour observation period. Patients enrolled over 10 month period.
Location	USA
Outcomes measures and effect sizes	Amount of meperidine received: The patients in the ketorolac group received an average of 231 ± 92 mg meperidine during the four hour observation period while those in the placebo group received an average of 250 ± 85 mg (p = 0.61) Pain rating (VAS):

	The amount of pain gradually decreased in the patients in each group over the four hours. The total relief of pain score was similar between the ketorolac group (44 ± 34) and placebo group (37 ± 31, p = 0.49). Adverse events: There were no noted side effects or adverse events in either group. Patient opinion and rate of admittance: 11/12 (92%) patients in the ketorolac group stated that they would want the drug at a future ED visit, whereas 7/12 (58%) in the placebo group felt that they would want the drug again (p = 0.08). 4/12 patients in the ketorolac group were admitted to the hospital for continuation of therapy, whereas 3/12 in the placebo group required admission (p = 0.50).
Authors' conclusion	The use of a single IM dose of ketorolac on presentation to ED did not significantly reduce the total amount of meperidine given for the treatment of sickle cell vaso-occlusive crisis.
Source of funding	Supported by Biomedical Research Support Grant
Comments	The study medication was assigned in accordance with a computer-generated randomisation schedule, and the drugs were administered in identical syringes. A 40% reduction in total narcotic requirement over four hours was considered to be a clinically significant difference. A sample size of 12 patients in each group allowed for a power of 0.8 to detect a difference of 40% in meperidine requirement between the two groups.

Table 39 Evidence table for Griffin et al (1994)

Bibliographic reference (Ref ID)	Griffin et al 1994 (Ref ID: 2184)
Study type & aim	Double blind, randomised study/ To examine whether the administration of high doses of corticosteroids early in a vaso-occlusive crisis will lessen the duration or severity of pain
Number and characteristics of patients	Total: 36 patients (with 56 episodes of pain). During 30 episodes the patients received placebo and during 26 episodes they received methylprednisolone. One patient received both drugs during separate episodes. Exclusions: Patients were excluded if pain had been present for more than 4 days before admission, if a bacterial infection was suspected or if ACS was present. Fever was not a reason for exclusion. Inclusions: Patients less than 21 years old who had sickle cell disease and were being followed in the comprehensive sickle cell clinic at Children's Medical Centre of Dallas who had acute pain that remained severe despite management at home and in the emergency department with fluids and analgesics. Patient characteristics: 27 patients (who had 44 episodes) had sickle cell anaemia, 7 (8 episodes) had SC and 2 (4 episodes) had S-Th. Their ages ranged from 2 to 19 years (mean 7.7 years). The 2 groups were balanced in terms of sex, type of haemaglobinopathy and duration of pain before hospitalisation but a large proportion of younger patients were randomly assigned to receive methylprednisolone (p = 0.016). 54 additional hospitalisation were deemed ineligible (see paper for full reasons).

Monitoring information and definitions	Monitoring: patients were placed on cardiac monitors and received IV fluids (5% dextrose with 0.45% saline) at a maintenance rate. Patients were monitored for potential toxic reactions. Pain scales: There is no specific mention of pain ratings
Intervention	Drug: Methylprednisolone Dose: two doses (15 mg per kg of body weight-maximum of 1000 mg) Route: IV given over 30 minutes Timing: The first dose was administered as soon as possible after admission and the second 24 hours later Other pain relief: Morphine sulphate (0.1 mg per kg per dose) given by intravenous bolus injection as often as every 2 hours when needed for moderate to severe pain. If the pain was poorly controlled at any time during the hospitalisation, the dose of morphine was increased to 0.15 mg per kg. If pain was severe after 24 hours of hospitalisation and the patient had received 8 or more bolus injections of morphine, the protocol allowed the use of a continuous infusion of morphine at the discretion of the physician. After the pain had stopped intravenous morphine was stopped and oral acetaminophen with codeine was given as needed.
Comparator	Drug: Saline placebo Dose: two doses (15 mg per kg of body weight-maximum of 1000 mg) Route: IV given over 30 minutes Timing: as above Other pain relief: as above
Length of follow up	Not specifically reported
Location	USA
Outcomes measures and effect sizes	Duration of inpatient analgesic therapy (age-adjusted): When all 56 episodes were included in the analysis, the age-adjusted duration of inpatient analgesic therapy was significantly longer for patients who received placebo than those who received methylprednisolone (mean 71.3 vs. 41.3 hours, p = 0.03). 7 episodes were complicated with ACS (3 in methylprednisolone group and 4 in placebo). When these episodes were excluded from the analysis the age-adjusted difference remained significant (mean 31.0 vs. 62.5 hours, p = 0.01). Atypical episodes were identified-episodes were evaluated for factors that could have biased the results in favour of the intervention group. One patient was enrolled during 6 episodes and received placebo in 5/6 of these episodes. Her painful episodes tended to be longer than average, thus all 6 episodes were eliminated in the second separate analysis. Short episodes (hospital stay < 24 hours) tended to cluster in the intervention group-this occurred in a total of 5 patients and it was unclear whether such rapid improvement in pain symptoms could be due to effects of glucocorticoid, thus these 5 episodes were also removed leaving 38 episodes. For these patients, the duration of analgesia remained significantly different (mean 53.6 hours in placebo vs. 35.8 hours in intervention group, p = 0.012 Use of morphine During 10 of the 56 episodes (7 in placebo and 3 in intervention, p = 0.1) a continuous infusion of morphine was required to control pain. After exclusion of those patients, the intervention group required on average fewer morphine injections (6.5 doses per episode) than those who received placebo (8.7 doses per episode) and received less morphine (0.82 vs. 0.97 mg per kg). These differences were not statistically significant. Readmittance:

	Patients were readmitted for recurrent pain within 2 weeks of discharge (one patient from placebo, 4 patients from intervention) Complications: No complications were observed during the study related to corticosteroid use
Authors' conclusion	Corticosteroids are promising as an adjunct to supportive therapy for painful episodes in children and adolescents with sickle cell disease.
Source of funding	Supported by grants from the National Institutes of Health and by the Sickle Cell Research Fund at Children's Medical Centre
Comments	Patients were randomly assigned in a double blind fashion to receive the study drug or placebo. Sealed, opaque envelopes were arranged in a computer generated random order and opened sequentially by the pharmacist to determine the patient's treatment assignment. The medications were prepared by the pharmacist, packaged identically and delivered marked 'study medication' to the bedside so that carers were blinded to treatment group. All 56 episodes were included in the analysis.

Table 40 Evidence table for Bartolucci et al (2009)

Bibliographic reference (Ref ID)	Bartolucci et al 2009 (Ref ID: 227)
Study type & aim	Double blind, placebo controlled, randomised study/ To compare ketoprofen to placebo for adults with SCD and severe VOC requiring hospitalisation
Number and characteristics of patients	Total: 54 patients were hospitalised for 66 VOC episodes. 52 (26 retained for analysis in each group). 33 were randomised to each group (14 treatment failures, 8 given blood transfusions, 5 had ACS and 1 had sepsis). Exclusions: VOC lasting longer than 72 hours or less than 24 hours, parenteral hydration longer than 24 hours, blood transfusion during the previous month, and NSAID intake during the previous 7 days, pregnancy, a history of drug abuse, hypertension, fever greater than 39 degrees, presence of ACS, severe anaemia requiring blood transfusion, psychiatric disorder, NSAID or ketoprofen allergy or contraindication, or peptic ulcer. Patients taking certain medications the week before enrolment were also excluded (e.g. valporic acid, aspirin-please see paper for full list). Inclusions: Homozygous SCD patients who were at least 15 years of age and a severe VOC requiring hospitalisation. Patients could be enrolled more than once if their hospitalisations were separated by at least one month. Patient characteristics: 34 men and 20 women, mean age in placebo 27 and 26 in ketoprofen group. No significant differences between treatment groups and no trend to significance were found (in terms of BMI, VOC duration before inclusion, laboratory values).
Monitoring information and definitions	Severe VOC: pain or tenderness affecting at least one part of the body that required opioids and was not attributable to other causes. Termination of VOC: when at least 3 of the 4 following criteria was met: absence of fever for 8 hours, absence of pain progression and no requirement of IV infusion of opioid analgesics for the last 8 hours, patient able to walk or move without pain, or absence of spontaneous pain with CPS of 1 or less. Success rate: percentage of VOC terminated without recourse to transfusion or complications. Treatment failure: ACS or need for blood transfusion because of severe complication, uncontrolled anaemia, uncontrolled VOC for longer than 5 days or sepsis.

<table>
<tr><td></td><td>Monitoring: VAS was recorded by a nurse every 4 hours and CPS every 12 hours.
Pre-Study: No details specifically reported
VAS Pain: Pain was assessed with VAS (0mm = no pain and 100mm = worst possible pain)
Categorical pain score (CPS): ranging from 0-3 points (0 = no pain or residual pain without the need for analgesia, 1 = mild pain, no pain increase upon mobilisations, 2 = moderate pain, increased by mobilisation, 3 = severe pain with disability)</td></tr>
<tr><td>Intervention</td><td>Drug: Ketoprofen
Dose: 300 mg/day for 2 days with a programmable pump then 100 mg of oral ketoprofen (100mg every 8 hours) for the next 3 days
Route: continuous IV infusion
Procedure: Other adjunctive treatment was standardised, including bed rest, fluid replacement with 5% glucose infusion (50mL/kg/day, < 3L), oral alkali water (1L/day), folic acid and analgesia (see other pain relief).
Timing: No further details reported
Other pain relief: with morphine and IV proparacetamol (acetaminophen 2g every 8 hours for 48 hours then 1g every 8 hours. Morphine was administered at 0.1mg/kg every 5 minutes until pain relief was achieved, followed by continuous morphine infusion at an initial dose of 2mg/hour with repeated pulses until pain was well controlled.</td></tr>
<tr><td>Comparator</td><td>Drug: Physiologic saline
Dose: Not specifically reported
Route: with syringe pump
Procedure: as above
Timing: No further details reported
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>5 days (treatment) 14 days (follow-up)</td></tr>
<tr><td>Location</td><td>France</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>VOC duration from inclusion (hours):
For the 52 assessable VOCs, no significant difference (p = 0.61) was found with comparable median durations for the 2 groups (placebo = 50, IQR 36-103, ketoprofen = 51, IQR 35.5-87). The day-by-day success rates were also comparable between groups (p = 0.56)
Other outcomes:
<table>
<tr><th>Treatment impact</th><th>Placebo (n=26)</th><th>Ketoprofen (n=26)</th><th>P-value</th></tr>
<tr><td>Morphine dose, median (IQR) mg</td><td>88 (52.5-262.5)</td><td>110 (46-195)</td><td>0.64</td></tr>
<tr><td>Total CPS (average of daily mean value), median (IQR)</td><td>0.4 (0.2-0.7)</td><td>0.4 (0.2-0.7)</td><td>0.46</td></tr>
</table>
</td></tr>
</table>

	Total VAS score (average of daily mean value), median (IQR) mm	9.6 (5.8-33.2)	12.6 (4.8-23.2)	0.50

Readmittance:

Among the 52 VOC's discharged, 4 ketoprofen group and 5 placebo group patients were readmitted (p = 1)

Adverse events:

Adverse event	**Placebo (n=33)**	**Ketoprofen (n=33)**
Abdominal pain	1	0
infection	0	2
Constipation	2	0
Epigastralgia	2	1
Facial edema	1	0
Fever	5	5
Hepatic cytolysis	1	0
Myocardial repolarisation abnormality	0	1
Nausea/vomiting	3	4
Pruritus	2	2
Somnolence	1	0
Tachycardia	1	0
Urinary retention	0	1
Total adverse events	19	16

Authors' conclusion	Author's concluded that although ketoprofen was well tolerated, it had no significant efficacy as treatment of VOC requiring hospitalisation and that these findings argue against its systematic use in this setting.
Source of funding	None reported.
Comments	Patients in whom treatment failed were secondarily censored: their data on pain were not taken into account for the analysis of evolution of pain intensity.

Table 41 Evidence table for Al-Jama et al (1999)

Bibliographic reference (Ref ID)	Al-Jama et al 1999 (Ref ID: 3521)

<table>
<tr><td>Study type & aim</td><td>Double blind, randomised study/ To test the efficacy and safety of isoxsuprine in the treatment of SCD painful crises.</td></tr>
<tr><td>Number and characteristics of patients</td><td>Total: 43 patients experiencing 44 episodes of pain (23 in isoxsuprine and 21 in meperidine group)
Exclusions: Evidence of infection or temperature >38.3 degrees, pregnancy or possibility of conception and lactation, recent arterial haemorrhage, use of β-blockers and likelihood of patient receiving general anaesthesia in the next 24 hours.
Inclusions: Patients 12 years or older with SCD (homozygous sickle cell disease or S-Th) presenting to the emergency department during the day with muscoskeletal painful crisis
Patient characteristics: There were 16 males and 7 females in isoxsuprine group and 18 males and 3 females in the meperidine group. The mean age was 18.5 years and 21.6 years in both groups respectively. There were no statistically significant differences among the two groups in terms of sex, age, height or weight.</td></tr>
<tr><td>Monitoring information and definitions</td><td>Monitoring: Assessment was done at 30 minutes, 60 minutes, 2 hours, 6 hours, and 24 hours post treatment
Pre-Study: No specific pre-study condition were reported
Pain scales: severity of pain was assessed on a VAS from 0-10 (0 indicating absence of pain, 10 indicating maximum pain experienced).
Degree of mobilisation: 0 = asymptomatic, 1 = symptomatic, fully ambulatory; 2 = symptomatic, in bed <50% of the day; 3 = symptomatic, in bed >50% of the day; 4 = confined to bed.</td></tr>
<tr><td>Intervention</td><td>Drug: Isoxsuprine
Dose: 5mg for patients <60 kg and 10mg for patients >60 kg
Route: IM
Procedure: All patients received IV fluids in the form of 5% dextrose alternating with normal saline at a rate of 120 cc/hour
Timing: injections were given every 4 hours for 24 hours. After 24 hours further management was left to the treating physician.
Other pain relief: During the 24 hours, any need for extra analgesics were assessed and recorded.</td></tr>
<tr><td>Comparator</td><td>Drug: Meperidine
Dose: 50mg for patients <60kg and 100mg for patients >60 kg
Route: IM
Procedure: as above
Timing: as above
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>24 hours</td></tr>
<tr><td>Location</td><td>Saudi Arabia</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Pain assessment and mobilisation:
<table>
<tr><th></th><th>Isoxsuprine group</th><th>Meperidine group</th><th>P-value</th></tr>
</table>
</td></tr>
</table>

	Pain score | | | 0 min | 10** | 10** | 0.01 30 min | 8 ± 2 | 6 ± 2 | 0.01 60 min | 7.6 ± 2 | 6 ± 2.5 | 0.05 2 hours | 7.2 ± 2.3 | 6.5 ± 3 | 0.48 6 hours | 6 ± 3 | 5 ± 3 | 0.3 24 hours | 5 ± 3 | 5 ± 3 | 0.9 Mobilisation score | | | 0 min | 3 ± 0.3 | 3 ± 0.4 | 0.7 24 hours | 2.6 ± 0.9 | 2.7 ± 0.6 | 0.8 **maximum pain for the present painful episode The control of pain was better with conventional treatment (meperidine) only at 30 and 60 minutes. Duration of crisis and hospitalisation: | **Isoxsuprine group** | **Meperidine group** | **P-value** Median crisis (range) | 24 (8-120) | 48 (24-168) | 0.44 Median hospitalisation (range) | 72 (24-288) | 72 (24-216) | 0.7
Authors' conclusion	This study confirms the potential effectiveness of this (Isoxsuprine) relatively safe drug for the treatment of acute painful crises of SCD.
Source of funding	No source of funding is reported.
Comments	One pharmacist was responsible for the preparation of the study drugs and the drugs were masked so that looked alike. Each set was given a code number which was known only to the pharmacist. The evaluator would pull a number from an envelope and the corresponding set of medication was dispensed.

Table 42 Evidence table for Van Beers et al (2007)

Bibliographic reference (Ref ID)	Van Beers et al 2007 (Ref ID: 582)
Study type & aim	Prospective, randomised, controlled trial (some patients crossed over)/ To determine the efficacy of PCA in VOC

Number and characteristics of patients	Total: 25 episodes of VOC in 19 patients (13 episodes in CI morphine, 12 in PCA morphine). Patients who met the inclusion criteria on a subsequent admission were crossed over to the alternative study arm. Of the six patients who crossed over, 4 received PCA and 2 received CI as initial treatment. Exclusions: Patients already receiving opioids for more than 24 hours or patients that were allergic to or intolerant to morphine. Inclusions: SCD (Hb SS, Hb SC, Hb $S\beta^0$, Hb $S\beta^+$), the presence of an episode of pain caused by VOC necessitating treatment with IV morphine, age more than 17 years. Patient characteristics: The baseline characteristics between the two groups were comparable in terms of sex, age, hydroxyurea treatment, haemoglobin genotype (no statistical comparisons are reported). Median age in the continuous infusion (CI) group was 25 years and 27 years in the PCA morphine group. There were 7 females in each group. Homozygous SCD was the most common genotype in both groups (8/13 and 8/12 in the CI and PCA group respectively). The mean time between first and second inclusion was 5 months. Leukocyte count (median 15.2, IQR 11.7-17.8 vs. 11.3, 7.9-13.4) was higher in the CI group.
Monitoring information and definitions	Pre-Study: All patients received a pain flow chart on the out patients clinic. With use of this flow chart, patients self-administer pain medication starting with 500 mg acetaminophen six times daily and adding 50 mg diclofenac three times daily, when needed. To be admitted for IV morphine treatment, pain scores had to be more than 4 during at least 4 hours with maximum self-administered pain medication. Episode of VOC: the occurrence of pain in the extremities, back, abdomen, chest or head that led to a clinic visit and could not be explained except by SCD. Pain scales: 11 point verbal response scale (0 = no pain, 10 = worst pain). Perceived pain intensity, importance of pain control and perceived control of pain were also assessed with a VAS, with 0mm designated 'not at all important' or 'not at all under control' and 100mm 'very much important' or 'completely under control' Adequate level of pain relief: A pain score of 5 or less on the 11 point verbal response scale was accepted as an adequate level of pain relief. Mean pain intensity (during treatment): average verbal response scores (collected 4 times a day) Difference in pain relief: The change between a single pain measurement on a VAS at baseline and a single measurement 2 days after treatment (0mm = no pain, 100mm = worst pain). Measurement of side effects: scored daily on an 11 point scale (0 = no symptoms, 10= worst symptoms)
Intervention	Drug: Morphine Dose: Single bolus injection of 5mg followed by PCA bolus of 0.01 mg/kg. Maximal one bolus every 5 minutes could be administered (a lock out of 5 minutes). If this dosage did not result in adequate pain relief, the bolus dose was increased to 0.02 mg/kg with a lockout of 5 minutes. Route: PCA (perfusor fm, Braun, Melsungen, Germany). The device allowed patients to self-administer an IV bolus of morphine by pressing a button attached to their bed. Procedure: Patients in the PCA group did not receive any continuous infusion as well as the self-administered boluses. Other pain relief: all patients received additional oral pain treatment consisting of 500 mg acetaminophen six times daily and 50 mg diclofenac three times daily during the whole admission. Patients with contraindications or intolerance for diclofenac received 50 mg tramadol.
Comparator	Drug: Morphine Dose: Single bolus injection of 5mg followed by continuous infusion (CI) of 0.03 mg/kg/hr. After pain assessment by the attending nurse, the morphine dose was increased when needed with cumulative steps of 1 mg/hr if pain scores were 5 or lower or at the patient's request.

<table>
<tr><td></td><td>Route: continuous infusion
Procedure: No additional information reported
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>Two days after treatment</td></tr>
<tr><td>Location</td><td>The Netherlands</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Morphine dose, adverse events and pain score:
<table>
<tr><th></th><th>CI-Morphine (median and IQR)</th><th>PCA Morphine (median and IQR)</th><th>P-value</th></tr>
<tr><td colspan="4">Morphine consumption</td></tr>
<tr><td>Morphine dosage (mg/hr)</td><td>2.4 (1.4-4.2)</td><td>0.5 (0.3-0.6)</td><td>0.001</td></tr>
<tr><td>Total morphine dosage</td><td>260 (204-529)</td><td>33 (10-68)</td><td>0.018</td></tr>
<tr><td colspan="4">Pain</td></tr>
<tr><td>Least verbal response pain score</td><td>4.2 (3.1-5.1)</td><td>4.2 (3.4-5.8)</td><td>0.14</td></tr>
<tr><td>Mean pain score[a]</td><td>4.9 (3.9-5.8)</td><td>5.3 (4.5-6.9)</td><td>0.09</td></tr>
<tr><td>Worst Verbal response pain score</td><td>5.8 (4.5-6.2)</td><td>6.3 (5.5-7.8)</td><td>0.39</td></tr>
<tr><td colspan="4">Mean side effect score and pain (AUC)[b]</td></tr>
<tr><td>Nausea</td><td>18 (3-55)</td><td>11 (3-21)</td><td>0.045</td></tr>
<tr><td>Constipation</td><td>45 (36-59)</td><td>30 (10-40)</td><td>0.021</td></tr>
<tr><td>Pruritus</td><td>14 (0-28)</td><td>5 (0-25)</td><td>0.42</td></tr>
<tr><td>Sedation</td><td>12 (6-33)</td><td>18 (0-20)</td><td>0.52</td></tr>
</table>
[a]Mean verbal response pain score
[b] Symptoms of side effects are presented as area under the curve (AUC) during treatment
The differences in morphine consumption may be partly explained by a relevant, but not statistically significant, reduced duration of morphine administration in the PCA group compared with the CI group (4.5, 3.3-6.0 days vs. 7.0, 5.0-8.5 days; p = 0.21), which was directly correlated to the total morphine dosage (p < 0.001). The patients in the PCA group pressed the button to self-administer a dose of morphine on average 14 (9-16) times a day.
Inadequate pain relief:
6 of the patients in the PCA group and 5 in the CI group needed a dose increase because of inadequate pain relief.
Admission duration:
The median duration of admission in the PCA group was 6.0 (4.3-9.3) days and in the CI group 9.0 (6.0-12.0) days (p = 0.15)
Pain and quality of life:
<table>
<tr><th></th><th>Baseline</th><th>Change after 2 days</th><th>P value*</th></tr>
</table></td></tr>
</table>

	Pain	**CI**	**PCA**	**CI**	**PCA**	
	Pain score (VAS)	59 (51-85)	72 (63-84)	-24 (-57 to -11)	-38 (-52 to 4)	1.00
	Importance of pain control (VAS)	98 (93-100)	98 (69-98)	-12 (-29 to -1)	2 (-7 to 10)	0.02
	Perceived pain control	39 (13-53)	48 (19-52)	22 (-8 to 44)	15 (-32 to 51)	0.79
	Quality of life[a]					
	Physical health summary	31 (23-37)	24 (21-36)	0 (-5 to 12)	1 (-7 to 9)	0.94
	Mental health summary	40 (34-56)	44 (37-56)	4 (-7 to 14)	4 (-2 to 9)	0.94
	[a] Short Form Health Survey (SF36) * P-value of difference in change after 2 days between CI and PCA					
Authors' conclusion	This study shows that morphine administration with PCA lead to markedly lower morphine consumption than dose-adjusted CI of morphine while both methods resulted in comparable pain relief. PCA should be considered to be the first choice in morphine administration to patients with SCD.					
Source of funding	No source of funding is reported.					
Comments	Randomisation was performed in blocks of 6 with closed envelopes, containing the designated morphine delivery regimen. Data were analysed on an intention to treat basis.					

Table 43 Evidence table for Gonzalez et al (1991)

Bibliographic reference (Ref ID)	Gonzalez et al 1991 (Ref ID: 2425)
Study type & aim	Randomised trial/ To assess morphine sulphate administration by intermittent IV injections (Int-IV) vs. patient-controlled analgesia (PCA) in patients in the emergency department (ED) with sickle cell crisis pain
Number and characteristics of patients	Total: A total of 15 cases were evaluated in each of the two treatment groups (10 patients were randomised to each group) for phase 1. In phase 2, a total of 23 cases were evaluated in the Int-IV group and 17 cases were evaluated in the PCA group (The Int-IV group consisted of 12 patients and there were 13 patients in the PCA group). 5 patients in the Int-IV group and 4 patients in the PCA group participated in phases 1 and 2. Patients who participated in phase 1 were maintained in their original treatment randomisation group during phase 2. Exclusions: history of drug or alcohol abuse, allergy to morphine, pregnancy or long-term use of narcotic analgesia. Inclusions: All patients 18-65 years of age who presented to the ED with SCC pain were considered for inclusion in the study. Patient characteristics: PHASE 1: For the Int-IV group there were 6 females and the mean age 28.3 ± 7.3 years. For the PCA group there were 6 females and the mean age was 33.9 ± 12.5 years (p = 0.056 for age). During the 24 hours prior to admission into the study, 46% (n=7) of cases in the Int-IV group and 43% (n=6) of cases in the PCA group had used non-narcotic analgesia, whereas oral narcotics were used by 20% (n=3) of cases in the Int-IV group and 15% (n=2) of those in the PCA group.

	PHASE 2: For the Int-IV group there were 7 females and the mean age 28.4 ± 5.9 years. For the PCA group there were 8 females and the mean age was 26.8 ± 8.1 years (p = 0.154 for age). During the 24 hours prior to admission into the study, 36% (n=8) of cases in the Int-IV group and 28% (n=5) of cases in the PCA group had used non-narcotic analgesia, whereas oral narcotics were used by 18% (n=4) of cases in the Int-IV group and 22% (n=4) of those in the PCA group.
Monitoring information and definitions	Pre-Study: All patients were placed at bed rest during their 8 hour treatment and observation period in the ED. IV 5% dextrose and 0.45% saline were infused at 150 mL/h. Patients assigned to the PCA group were instructed on self-administration of parenteral morphine via the PCA pump prior to participation in the study. Visual LPS scale: 100mm (0 = no pain, 100 = worst pain imaginable) VPS: 0 indicating no pain and 10 being worst pain Level of alertness (LA): Assessed by the nurse (0 = awake and alert, 1 = awake and not alert, 2 = intermittent light sleep, 3 = sound sleep, 4 = deep sleep and arousable with difficulty) Adverse reaction: defined as the development of nausea, vomiting, a dermatological reaction, hypotension (systolic blood pressure < 90mm Hg), respiratory depression, (respiratory rate < 10 respirations per min) or documented LA = 4 any time during the study Overall satisfaction with the drug: 1 = poor to fair, 2 = good to excellent
Intervention	PHASE 1 Drug: Morphine sulfate Dose: 2 mg IV bolus followed by 1 mg IV with a 6 minute lock-out via PCA Route: PCA pump (Stratofuse PCA, Baxter Healthcare Corp) is an electrified pump deigned to deliver on demand doses, continuous infusion or a combination of the two. Procedure: Drug was injected in the patient's primary IV line when the patient depressed the control button. If the button was depressed during the lock-out period, the drug was not delivered but the event was documented as an attempted dose. Patients were maintained on the study regimens until their pain was controlled. Other pain relief: If the initial regimens failed to provide adequate pain relief (LPS < 50 mm) within a minimum of 3 hours, the dose of morphine sulphate was increased to 6 mg IV in the Int-IV group and to 1.5 mg with a 6 minute lock-out in the PCA group. No anxiolytics, tranquilisers or sedatives were allowed during the study period. Prochlororperazine (IM 10 mg) was permitted for nausea and vomiting and diphenhydramine hydrochloride (IV 25-50 mg) was allowed for dermatological reactions. PHASE 2 Phase 2 was similar to phase 1 but used a higher dose of morphine. During phase 2 the PCA group received a 5 mg morphine bolus followed by 2.7 mg with a 10 minute lock-out. If insufficient pain relief was obtained after a minimum of 3 hours, the doses were increased to 3.3 mg of morphine sulphate with a 10 minute lock-out.
Comparator	PHASE 1 Drug: Morphine sulfate

<table>
<tr><td></td><td>
Dose: 4 mg
Route: IV (intermittent IV injections)
Procedure: Drug was given every 30 to 60 minutes as needed to achieve and maintain a LPS below 50mm
Other pain relief: as above
PHASE 2
During phase 2, the Int-IV group received morphine sulfate, 8 mg IV every 30 to 60 minutes as need to maintain a LPS of less than 50mm. If insufficient pain relief was obtained after a minimum of 3 hours, the doses were increased to 10 mg of morphine sulfate every 30 to 60 minutes as needed
</td></tr>
<tr><td>Length of follow up</td><td>8 hour treatment and observation period in the ED</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>
PHASE 1 RESULTS:
Pain outcomes:
<table>
<tr><td></td><td colspan="3">Initial</td><td colspan="3">Final</td></tr>
<tr><td>Variable</td><td>Int-IV (control)</td><td>PCA</td><td>P-value</td><td>Int-IV (control)</td><td>PCA</td><td>P-value</td></tr>
<tr><td>LPS mm</td><td>90.7 ± 11.1</td><td>92.2 ± 11.9</td><td>0.76</td><td>32.2 ± 29.6</td><td>32.3 ± 31.8</td><td>0.934</td></tr>
<tr><td>VPS</td><td>8.6 ± 1.1</td><td>9.20 ± 0.94</td><td>0.469</td><td>3.9 ± 2.4</td><td>3.2 ± 2.7</td><td>0.580</td></tr>
</table>
Total number of doses of morphine:
The total number of doses of morphine administered was significantly less in the Int-IV group (6.5 ± 2.6) when compared to the PCA group (35.5 ± 23.5 mg, p = 0.0006). However, the total amount of morphine administered did not significantly differ (p = 0.623) between the Int-IV group (28.8 ± 13 mg) and the PCA group (35.5 ± 23.5 mg). A dosage increase was necessary in 53% of patients in the Int-IV group and in 33% of the patients in the PCA group (p = 0.269).
LOS and admission:
There was a trend toward a shorter average LOS in the ED for the Int-IV group (6.5 ± 2.6 hours) when compared with the PCA group (7.1 ± 3.6 hours, p = 0.083). the percentage of cases admitted to the ED because of unresolved pain crisis was 20% (n = 3) in the Int-IV group and 40% (n = 6) in the PCA group (p = 0.232)
PHASE 2 RESULTS:
Pain outcomes:
<table>
<tr><td></td><td colspan="3">Initial</td><td colspan="3">Final</td></tr>
<tr><td>Variable</td><td>Int-IV (control)</td><td>PCA</td><td>P-value</td><td>Int-IV (control)</td><td>PCA</td><td>P-value</td></tr>
<tr><td>LPS mm</td><td>91.3 ± 11.7</td><td>86.6 ± 14.9</td><td>0.393</td><td>39.5 ± 33.8</td><td>30.5 ± 35.7</td><td>0.829</td></tr>
<tr><td>VPS</td><td>8.8 ± 1.2</td><td>8.4 ± 1.9</td><td>0.355</td><td>4.2 ± 2.7</td><td>3.6 ± 3.4</td><td>0.793</td></tr>
</table>
Total number of doses of morphine:
</td></tr>
</table>

	While, the total number of morphine doses administered was significantly (p = 0.0002) higher with PCA than with Int-IV (11.6 ± 6.3 vs. 4.9 ± 2.0), the total amount of morphine sulfate administered did not significantly differ between Int-IV (41.0 ± 17.6 mg) and PCA (34.6 ± 20.9 mg) groups (p = 0.945). A dosage increase was required by 35% (n = 8) and 25% (n = 4) of cases receiving Int-IV and PCA respectively (p = 0.726). LOS and admission: The average LOS in the ED did not significantly differ (p = 0.352) between the Int-IV group (5.5 ± 1.6 hours) and the PCA group (5.7 ± 1.9 hours). The percentage of cases admitted to the ED because of unresolved pain crisis was 35% (n = 8) in the Int-IV group and 29% (n = 5) in the PCA group (p = 0.652) COMPARISON OF PHASE 1 vs. PHASE 2: Within the Int-IV group, there was a trend towards more morphine sulfate being administered during phase 2 (41.0 ± 17.6 mg) when compared with phase 1 (28.8 ± 13.0 mg, p >0.05). In the PCA group there was a significant reduction in the total number of morphine doses administered during phase 2 (11.6 ± 6.2) when compared to phase 1 (29.7 ± 16.6, p = 0.001), whereas the total amount of morphine sulfate administered was almost identical in phase 1 (35.3 ± 23.5 mg) and phase 2 (34.6 ± 20.9). the average LOS was significantly shorter during phase 2 (5.6 ± 1.9 hours vs. 7.1 ± 1.8 hours) in the PCA group (p = 0.02). Adverse events: PHASE 1: the incidence of adverse events was 53% and 47% in the Int-IV group and the PCA group respectively (p = 0.715). 4 patients (27%) in the Int-IV group and 3 patients (20%) in the PCA group required medication for nausea and vomiting (p = 1.00). Pruritus requiring treatment occurred in 1 patient in each treatment group. 1 patient in each group became difficult to arouse after treatment with morphine. PHASE 2: side effects were frequent in Int-IV group (65%) and the PCA group (56%, p = 0.571). Nausea and vomiting that required treatment developed in 10 (44%) of patients in the Int-IV group and 5 patients (31%) in the PCA group (p = 0.44). 6 patients in the Int-Iv group and 2 in the PCA group required treatment for pruritus (p = 0.43). 1 patient in the Int-IV group became difficult to arouse. Respiratory depression or clinically significant hypotension was not observed during the study.
Authors' conclusion	At both the high and low dose regimens, PCA is equally as safe and effective and may be used in place of Int-IV administration of morphine in the ED treatment of sickle cell crisis pain
Source of funding	Funded by a grant from Baxter Healthcare Corporation and the University Hospital Consortium
Comments	Method of randomisation not reported. 3 patients required discontinuation of treatment because of side effects

Table 44 Evidence table for Quari et al (2007)

Bibliographic reference (Ref ID)	Qari et al 2007 (Ref ID:599)
Study type & aim	A randomised, double-blind, clinical trial/ To test the safety and efficacy of a low-molecular-weight heparin (LMWH) tinzaparin for the management of acute painful VOC characteristic of sickle cell anemia (SCA).

<table>
<tr><td>Number and characteristics of patients</td><td>Total: 253 patients (127 in intervention group and 126 in control)
Exclusions: The presence of medical or surgical contraindications to LMWH, pregnancy, low platelet counts or impaired hemostasis on admission, complicated SCA, history of cerebral vascular accident, current aplasia, ACS, exchange transfusion, sequestration, anticoagulant therapy for other etiology, patients with painful crisis within the month before this admission and women on hormonal contraception.
Inclusions: SCA patients with SS disease admitted through the ED with painful crisis aged > 12 years
Patient characteristics: For the intervention group, the mean age was 22.8 ± 4.5 and 54% were female. In the control group, the mean age was 21.6 ± 3.8 and 50% were female (no statistical analyses were reported).</td></tr>
<tr><td>Monitoring information and definitions</td><td>Pre-Study: All patients received the same standard therapy consisting of hydration, and analgesia consisting of morphine
Acute painful crisis: the presence of bone pain with features typical of the painful crisis and not resulting from other pathology. The pain had to of sufficient severity to require narcotic analgesia (i.e. pain not relieved by simple analgesics such as acetaminophen).
Pain scales: Numerical pain scale (see paper Jaywant & Pai 2003)
Clinical improvement: achievement of a pain score < 2 reported by the patient on the numerical pain scale (NMS)
Overall duration of painful crisis: number of days needed for the pain to decline from the highest score to < 2 on the NMS
Major haemorrhage: overt haemorrhage associated with at least one of the following: death, the need for a transfusion of at least two units of packed red blood cells or a fall in haemoglobin > 2.0g/l as compared with baseline</td></tr>
<tr><td>Intervention</td><td>Drug: Tinzaparin
Dose: 175 anti-Xa IU/kg
Route: Subcutaneously
Procedure: Tinzaparin was given once daily for seven days
Other pain relief: Standard analgesia therapy of morphine (1 mg/h IV infusion) and rehydration with normal saline</td></tr>
<tr><td>Comparator</td><td>Drug: Placebo
Dose: no details reported
Route: similar to Tinzaparin group
Procedure: as above
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>7 days</td></tr>
<tr><td>Location</td><td>Saudi Arabia</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Outcomes:
<table>
<tr><th></th><th>Tinzaparin group (n = 127)</th><th>Control group (n = 126)</th></tr>
<tr><td>No of days with severest pain score on the NMS</td><td>1.28 ± 0.20*</td><td>1.74 ± 0.15</td></tr>
<tr><td>Duration of painful crisis (days)</td><td>2.57 ± 0.45*</td><td>4.35 ± 0.78</td></tr>
</table></td></tr>
</table>

	Total duration of hospitalisation (days)	7.08 ± 1.8*	12.06 ± 2.2
	Tinzaparin treated patients had significantly fewer total hospital days, overall days of crisis and days of severity pain score compared to the placebo treated patients. Adverse events: Tinzaparin treatment was associated with 2 minor bleeding events that were reported and treated by cessation of the Tinzaparin.		
Authors' conclusion	Tinzaparin, administered at its approved treatment regime, reduced the severity and duration of acute crisis of SCA.		
Source of funding	Source of funding is not reported.		
Comments	Method of randomisation is not reported		

Table 45 Evidence table for Adam-Graves et al (1997)

Bibliographic reference (Ref ID)	Adam-Graves et al 1997 (Ref ID: 1874)
Study type & aim	Randomised, double-blind, placebo controlled (phase II) pilot study/ To evaluate the safety and efficacy of poloxamer, formulated as RheothRx or placebo in adult patients experiencing an acute painful episode
Number and characteristics of patients	Total: 50 patients (28 were randomised to intervention and 22 to placebo) Exclusions: patients who are pregnant, have clinically active renal or hepatic disease, require daily use of narcotic analgesia, have more than 15 painful crises per year for the last 2 years, have a painful episode with life-threatening complication, have pain involving the chest, which was possibly pulmonary or cardiac in origin, have had a painful event requiring hospitalisation within the preceding 2 weeks and have received hydroxyurea in the preceding 3 months. Inclusions: patients with SCD (HbSS, HbSB, HbTh, HbSC) aged 15 years or older who have had at least one previous documented acute painful episode, have moderate or severe pain (lasting at least 4 hours but no longer than 18 hours) upon presentation to hospital and have acceptable medical history, physical examination and clinically accepted vital signs. Patient characteristics: The 2 treatment groups were comparable in terms of sex, age, weight, race, onset of the painful episode to start of the study drug. In the intervention group the median age was 25.0 (range 19-42) years, 46% were female and 89% had HbSS. In the control group, the median age was 26.5 (range 15-55), 55% were female and 96% had HbSS. There was an imbalance in the baseline pain score between the treatment groups; severe pain was present in 39% of patients receiving RheothRx and 64% of patients receiving placebo (all but 4 patients in the RheothRx group received parenteral analgesia, which may have altered their baseline scores (analyses have been adjusted).
Monitoring information and definitions	Pain intensity: evaluated by a 5 point scale (0 = no pain, 0.5 = residual soreness, 1 = mild pain, 2 = moderate pain, 3 = severe pain) Average pain intensity: average pain intensity over 168 hours (the 2 day dosing period and the 5 day post treatment period). If patients did not have pain intensity scores through 168 hours, the score for the last available pain assessment was carried forward to 168 hours. MEU: Morphine equivalent units (to compare the treatment groups with respect to quantity of analgesia given, the doses of all analgesics were converted into

<table>
<tr><td></td><td>MEU.
Duration of painful episode: time from initiation of study drug until the two criteria for termination are met (see below)
End of painful event: the end of an 8 hour period of no pain, residual pain, or mild pain and (2) at least 12 hours after the administration of parenteral analgesics.</td></tr>
<tr><td>Intervention</td><td>Drug: RheothRx injection (poloxamer 188)
Dose: 60 minute loading dose of 300 mg/kg followed by 47 hour maintenance infusion of 30 mg/kg/h
Route: IV infusion (2 stages) over 48 hours
Procedure: No other details provided
Other pain relief: Parenteral analgesia allowed during the study was meperidine, morphine and hydromorphone. Oral analgesia was restricted to NSAIDs, meperidine, acetaminophen, aspirin, codeine, oxycodone and/or any combination of these agents.</td></tr>
<tr><td>Comparator</td><td>Drug: RheothRx placebo (the vehicle for RheothRx injection)
Dose: as above
Route: as above
Procedure: as above
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>Minimum required duration of hospitalisation was 3 days (2 for infusion and 1 for post infusion observations and assessments)</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Efficacy outcomes (by subgroup):
<table>
<tr><th>Outcome</th><th colspan="3">Subgroup 1a (n = 49)</th><th colspan="3">Subgroup 2b (n = 45)</th><th colspan="3">Subgroup 3c (n = 31)</th></tr>
<tr><th></th><th>RheothRx (n=27)</th><th>Placebo (n=22)</th><th>P-value*</th><th>RheothRx (n=25)</th><th>Placebo (n=20)</th><th>P-value*</th><th>RheothRx (n=18)</th><th>Placebo (n=13)</th><th>P-value*</th></tr>
<tr><td>Duration of painful episodes (median hours)</td><td>67</td><td>80</td><td>0.182</td><td>60</td><td>88</td><td>0.122</td><td>44</td><td>80</td><td>0.025</td></tr>
<tr><td>Duration of hospitalisation** (median days)</td><td>5</td><td>6</td><td>0.258</td><td>5</td><td>7</td><td>0.202</td><td>5</td><td>7</td><td>0.111</td></tr>
<tr><td colspan="10">Total analgesic use</td></tr>
<tr><td>All analgesics (median MEU)</td><td>57 mg</td><td>159 mg</td><td>0.200</td><td>49 mg</td><td>169 mg</td><td>0.144</td><td>34 mg</td><td>145 mg</td><td>0.045</td></tr>
<tr><td>Parenterals only (median MEU)</td><td>47 mg</td><td>149 mg</td><td>0.220</td><td>40 mg</td><td>150 mg</td><td>0.130</td><td>27 mg</td><td>133 mg</td><td>0.022</td></tr>
</table>
[a] Intent to treat
[b] Excludes people with study drug infusion time < 24 hours
[c] Excludes people who did not receive full dose of study drug
* Adjusted p-value (for baseline pain) reported in evidence table. Unadjusted values are also reported in the paper but are not reported in this evidence table</td></tr>
</table>

** A 3 day minimum stay was required

Pain intensity (only subgroup 3-only this subgroup had pain intensity scores monitored until resolution of episode):

	Placebo (n = 13)	**RheothRx (n = 18)**	**P-value***	**P-value****
Pain intensity over 72 hours	2.0	1.1	0.034	0.056
Pain intensity over 168 hours	1.4	0.8	0.049	0.066

* T-test

** Linear model adjusted for baseline pain score

Medians of the average pain intensity scores for subgroup 3, Calculated as AUC/length of interval

Adverse events:

Adverse event	**RheothRx (n = 28)**	**Placebo (n = 22)**
Headache	6	5
Nausea	5	1
Pain: injection site	4	1
Pain: abdomen	3	2
Vomiting	3	2
Constipation	2	3
Infection urinary tract	1	2
Pharyngitis	2	0
Pruritus	2	0

Most of the adverse events were mild or moderate in intensity. One event was considered serious and attributable to the study medication (transient increase in serum creatinine concentration during infusion of RheothRx).

Authors' conclusion	RheothRx significantly reduced total analgesic use and pain intensity and showed trends to shorter duration of painful episode and total days hospitalisation. In patients with moderate to severe vaso occlusive pain, RheothRx was safe and may offer a therapeutic benefit.
Source of funding	Supported by Glaxo Wellcome Inc. (formally Burroughs Wellcome Co)
Comments	Trial conducted at 6 clinical centres

Table 46 Evidence table for Orringer et al (2001)

Bibliographic reference (Ref ID)	Orringer et al 2001 (Ref ID:1424)

<table>
<tr><td>Study type & aim</td><td>Randomised, double-blind, placebo controlled, intention to treat trial/ To compare the duration of painful episodes in patients with SCD treated with purified poloxamer 188 (PP188) to that of similar episodes experienced by patients who receive a placebo</td></tr>
<tr><td>Number and characteristics of patients</td><td>Total: 255 (127 were randomised to PP188 group and 128 to placebo group).
Exclusions: patients with clinically significant bleeding, chronic bacterial osteomyelitis, pregnancy or breastfeeding, inadequate venous access, history of major surgery (≤ 2 weeks prior), episode of pain requiring hospitalisation ≤ 2 weeks prior, current hospitalisation, participation in another study, enrolment in a hypertransfusion program, recent cerebrovascular accident or seizure, other complications,
Inclusions: patients with documented SCD who are aged 8-65 years with adequate liver and renal function. Patients will have sudden onset of acute pain involving ≥ 1 sites typical of vaso-occlusive pain, severe pain requiring parenteral analgesia.
Patient characteristics: Baseline characteristics were compared between the PP188 group and placebo group with respect to sex (59% vs. 59% female in each group respectively), ethnicity (98% African American in each group), age (mean 21.11 vs. 20.97), weight (58.29 vs. 58.66 kg), currently receiving hydroxyurea (21% vs. 23%), genotype (77% vs. 79% SS/Sβ^0Th). There were no significant differences in terms of time from onset of crisis to randomisation, time from admission to randomisation, time from randomisation to start of study drug infusion, length of study drug infusion, number of pain locations and baseline pain intensity (all p > 0.05).</td></tr>
<tr><td>Monitoring information and definitions</td><td>Pain: VAS pain assessment was obtained every 4 hours during treatment and through resolution of crisis or 5 days after infusion, which ever occurred first. VAS scale range 0-100 with higher scores indicating more pain.
Duration of crisis: measured from randomisation until all the following had been simultaneously achieved: (1) pain relief (pain score ≤40 maintained during 2 consecutive readings obtained 4 hours apart), (2) freedom from parenteral analgesic use (none in the preceding 12 hours), (3) ability to walk without difficulty (unless not able to walk prior to onset of crisis), (4) patients belief that the painful episode is over (defined as readiness for discharge with or without oral analgesic use).</td></tr>
<tr><td>Intervention</td><td>Drug: PP188
Dose: loading dose of 100 mg/kg for 1 hour followed by maintenance dose of 30 mg/kg per hour for 47 hours
Route: IV (dedicated to study medication)
Other pain relief: Parenteral analgesics were given IM or IV. NSAID use was not allowed during infusion of study drug or 12 hours following discontinuation. Concurrent therapy with hydroxyurea was allowed. Parenteral analgesia was limited to morphine, hydromorphone and meperidine. Oral analgesia was restricted to codeine, morphine, hydromorphone, oxycodone, acetaminophen and appropriate combinations of each.</td></tr>
<tr><td>Comparator</td><td>Drug: Saline solution
Dose: same volume and duration as intervention drug
Route: IV (dedicated to study medication)
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and</td><td>Mean duration of crisis:
<table>
<tr><th>Groups</th><th>PP188 (SD)</th><th>Placebo (SD)</th><th>P-value*</th></tr>
</table></td></tr>
</table>

effect sizes

All randomised patients (n = 255)	136.62 (41.38)	141.43 (41.90)	0.04
All treated patients (n = 249)	132.34 (41.42)	140.35 (42.39)	0.07
Patients concurrently receiving hydroxyurea (n = 54)	141.36 (37.04)	157.19 (27.58)	0.02
Patients ≤ 15 years old (n = 73)	127.07 (42.47)	148.58 (36.71)	0.01

*computed using Wilcoxon rank sum test

Kaplan-Meier analysis of proportion of patients remaining in crisis:

The rate of crisis resolution in the patients receiving hydroxyurea was significant (p = 0.01) as were the responses for children (p = 0.007).

Crisis resolution:

In PP188 treated patients, 65/126 achieved crisis resolution per the protocol definition compared to 45/123 placebo treated patients and this difference was statistically significant (p< 0.02). For patients receiving hydroxyurea, 12/26 treated with PP188 achieved crisis resolution. This was also significantly higher than the 4/12 placebo-treated patients (p = 0.02). Finally, the proportion of children who achieved crisis resolution was markedly higher in the PP188 group (22/37 vs. 10/36, p = 0.009).

Secondary outcomes:

Variable	**PP188 (n=126)**	**Placebo (n=123)**	**P-value***
Time to discharge (hours)			
All treated patients (n = 249)	148.86 (74.27)	152.86 (95.12)	0.71
Patients receiving concurrent hydroxyurea (n = 54)	142.77 (56.17)	179.36 (101.17)	0.11
Patients ≤15 years (n = 73)	150.59 (95.15)	154.57 (74.97)	0.84
VAS pain, U/h (0-168 h)			
All treated patients (n = 249)	7516 (4168)	7429 (4142)	0.87
Patients receiving concurrent hydroxyurea (n = 54)	7951 (3524)	8012 (3287)	0.85
Patients ≤ 5 years (n = 73)	7865 (4698)	9194 (4584)	0.23
Total analgesic use (MEU/kg)			
All treated patients (n = 249)	0.98 (2.00)	1.09 (1.99)	0.68
Patients receiving concurrent hydroxyurea (n = 54)	1.78 (3.77)	1.10 (1.07)	0.38
Patients ≤15 years (n = 73)	0.53 (0.41)	0.72 (0.75)	0.18

* Computed using Wilcoxon rank sum test for time to discharge and t test for pain intensity and analgesic use. All data are mean (SD)

Safety analysis:

There were no significant differences between the two treatment groups in the overall incidence of adverse events, for adverse events defined as serious or for adverse events involving any body system groups as a whole. There was no evidence of increased risk of bleeding in the PP188 treatment. There was one death due to pulmonary fat embolism in the PP188 group; the patient had not received study drug infusion for 3 days prior to death. The

	underlying cause of death was judged by investigator to be SCD, not study drug treatment. Renal function was not influenced by PP188 treatment. However, the group randomised to PP188 did exhibit a modest but statistically significant increase in levels of alanine aminotransferase and direct bilirubin, each returned to baseline level by 35 day follow-up visit.
Authors' conclusion	The decrease in the duration of vaso-occlusive crisis and increase in the proportion of patients able to achieve crisis resolution, particularly in children are very encouraging.
Source of funding	Funding for this study was provided by CyRx Corp (the company that developed PP188. They hired a contract research organisation Theradex Corp to manage all aspects of the design and co-ordination of this study.)
Comments	Patients enrolled at 40 different medical centres in the USA. Randomisation was carried out by a central procedure using dynamic randomisation method stratifying by site, genotype and use of hydroxyurea.

Table 47 Evidence table for Teuscher et al (1989)

Bibliographic reference (Ref ID)	Teuscher et al (Ref ID:2522)
Study type & aim	Randomised, double-blinded trial/ To investigate the efficacy and appropriateness of pentoxipyllin in the treatment of acute crisis.
Number and characteristics of patients	Total: children and adolescents. 37 patients with Hb SS (36 patients analysed) Exclusions: patients < 5 years of age, onset of painful crisis of less than 4 hours or greater than 48 hours, painful crisis within the last 14 days, previous other specific treatments for sickle cell crisis, severe clinically detectable bacterial infections, cardiovascular complications, haemoglobin < 3, 4mmol/L, pregnancy, known drug misuse, severe renal or hepatic insufficiency, hypertension, oral contraceptives, known sensitivity for methylxanthines and participation in other clinical trials within the previous 4 weeks. Inclusions: non complicated painful crisis in people > 5 years old with evidence of severe painful crisis necessitating immobilisation due to pain, with an onset 48 hours or less before admission. Patient characteristics: Demographic (age, sex) and anthropometric (weight) data, clinical and laboratory parameters at entry were similar in both groups (details not provided in the paper). At baseline, pain intensity and level of immobility were comparable. 83% of patients had some drug treatment (chloroquine, folic acid) before presenting at the clinic.78% (n = 28) received analgesic medication as an adjunctive treatment, mostly acetaminophen or codeinphosphate.
Monitoring information and definitions	Sickle cell crisis: sudden onset of pain involving one or more sites, typical of the patient's usual crisis for which there was no other explanation. Local pain: 0 = no local pain, 1 = deep palpation painful, 2 = superficial painful, 3 = pain prevents palpation Local impairment of movement: 0 = no limitation, 1 = limited movements, 2 = active on request, 3 = passive movements Overall impairment: 0 = normal activity (moves in bed, slight pain), 1 = pain moving, (cautious moves; severe pain) 2 = changing position, 3 = total immobilisation Duration of crisis: time from onset of crisis until end of crisis Duration of therapy: onset of IV treatment until end of crisis End of crisis: absence of limitations in movements with only slight pain (score 1), interpreted as residual bone pain, and discontinued analgesia for at

<table>
<tr><td></td><td>least 12 hours</td></tr>
<tr><td>Intervention</td><td>Drug: Pentoxiphyllin
Dose: 20mg/kg/day in 0.9% NaCl (maximum daily dose 1600 mg)
Route: IV
Procedure: Each patient received an IV infusion of study medication every 8 hours. Treatment continued for 5 days or until the end of crisis, which ever was shorter. The IV volume was adjusted to clinical requirements.
Other pain relief: Analgesic therapy was standardised. Choice was limited to a single drug, either acetaminophen (50 mg/kg/day, max 3 mg per day) or codeinphosphate (4 mg/kg/day) or parenteral morphine derivatives (buphenorphine). Analgesia was discontinued 12 hours before the study medication was stopped. All participants received a curative dose of chloroquine as is standard practice in the treatment of acute crisis.</td></tr>
<tr><td>Comparator</td><td>Drug: placebo containing 0.9% saline in matching vials
Dose: as above
Route: IV
Procedure: as above
Other pain relief: as above</td></tr>
<tr><td>Length of follow up</td><td>Not specifically reported</td></tr>
<tr><td>Location</td><td>West Africa</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Mean duration (SD) of painful sickle cell crisis and therapy:
<table>
<tr><th>Duration of:</th><th>Pentoxiphyllin (n = 18)</th><th>Placebo (n = 18)</th><th>Difference mean (SE)</th><th>95% CI</th><th>P-value</th></tr>
<tr><td>Crisis (hours)</td><td>77.6 (40.2)</td><td>102.4 (25.3)</td><td>24.8 (11.2)</td><td>2.0 to 47.5</td><td>0.03</td></tr>
<tr><td>Therapy (hours)</td><td>58.6 (28.7)</td><td>80.0 (24.7)</td><td>21.4 (8.9)</td><td>3.3 to 39.6</td><td>0.02</td></tr>
</table>
The paper also reports a survival analysis of probability for crisis to be terminated. Evaluation over time of the drugs' efficacy showed that the intervention improved the cure rate within the first 48 hours of treatment. Both treatments mobility and decreased pain scores significantly ($p < 0.05$) by 48 hours in comparison to baseline. The proportion of patients cured within the first 48 hours was significantly higher in the intervention group (intervention: 10/18, placebo: 2/18, p= 0.002).
Adverse events:
Adverse events observed in 9 patients (6 in intervention, 3 in placebo, $p > 0.10$) were fever, shivering and pruritus.</td></tr>
<tr><td>Authors' conclusion</td><td>Pentoxiphyllin seems to be the only drug showing safe efficacy in the management of acute vaso-occlusion in sickle cell disease. Our evidence of efficacy and safety has to be corroborated through trials in other healthcare settings.</td></tr>
<tr><td>Source of funding</td><td>No sources reported.</td></tr>
<tr><td>Comments</td><td>No details of randomisation method reported.</td></tr>
</table>

Table 48 Evidence table for Hardwick et al (1999)

Bibliographic reference (Ref ID)	Hardwick et al 1999 (Ref ID:1659)
Study type & aim	Prospective, double-blind, randomised study/ To determine if a single dose of IV ketorolac given upon presentation to the emergency department would reduce the total dose of morphine required by the child in a vaso-occlusive pain crisis, decrease the rate of hospitalisation for these patients and decrease the rate of ED readmission for discharged patients
Number and characteristics of patients	Total: 29 patients were enrolled (7 enrolled more than once). The number of visits was 41. 22 patients received ketorolac and 19 received placebo. Exclusions: Patients with a known or suspected complication, an allergy to one of the study medications and those with a history of renal disease, peptic ulcer disease, bleeding disorder or use of analgesics or central nervous medications within 3 hours of enrolment. Inclusions: Patients aged between 5 and 17 years with sickle cell anaemia, who presented with pain crisis. Patients could be enrolled in the study more than once if their visits were separated by at least 1 month. Patient characteristics: There were no significant differences (all $p > 0.05$) between ketorolac group and placebo group in terms of mean age (11.3 vs. 12.2 years), mean weight (41 vs. 40.5 kg), gender (50% vs. 63% male), duration of pain (28 vs. 43 hours) and initial mean VAS score (5.86 vs. 5.43 cm).
Monitoring information and definitions	Monitoring: Vital signs including pulse, respirations, and blood pressure were taken at least every 60 minutes throughout the 6 hour observation period. Pain intensity: Patients rated the intensity of their pain on a 10 cm VAS scale at the beginning of the study and again every 60 minutes throughout the 6 hour observation period.
Intervention	Drug: Ketorolac Dose: 0.9 mg/kg Route: IV Procedure: $D_5$1/2 normal saline was administered at a rate of 3000 mL/m^2/day for all patients Other pain relief: All patient received 0.1 mg/kg IV morphine sulfate simultaneously with study medication. Additional doses of morphine sulfate were administered every 2 hours based upon pain intensity rates on the VAS. In the absence of a sliding scale for titration of narcotic dose to degree of pain relief, patients with pain intensity score below the initial pain intensity rating received 0.1 mg/kg of morphine sulfate. Patients without pain were not given further morphine sulfate unless the pain recurred. Other analgesics or sedatives were not administered.
Comparator	Drug: Saline placebo Dose: as above Route: IV Procedure: as above Other pain relief: as above
Length of follow up	6 hour observation period.
Location	USA

<table>
<tr><td>Outcomes measures and effect sizes</td><td>
<u>Morphine sulfate received:</u>
The patients in the ketorolac group received an average of 0.28 ± 0.08 mg/kg of morphine sulfate while those in the placebo group received an average of 0.32 ± 0.08 mg/kg (p = 0.118).
<u>Mean VAS pain scores (2 decimal places):</u>
<table>
<tr><th>Time</th><th colspan="2">Mean VAS</th><th colspan="2">± SD</th><th rowspan="2">t</th><th rowspan="2">P-value</th></tr>
<tr><th></th><th>Placebo</th><th>Ketorolac</th><th>Placebo</th><th>Ketorolac</th></tr>
<tr><td>0 hours</td><td>5.43</td><td>5.86</td><td>2.23</td><td>2.23</td><td>0.132</td><td>0.90</td></tr>
<tr><td>1 hour</td><td>4.45</td><td>4.36</td><td>2.61</td><td>2.66</td><td>0.113</td><td>0.91</td></tr>
<tr><td>2 hour</td><td>4.98</td><td>4.39</td><td>2.46</td><td>2.95</td><td>0.692</td><td>0.49</td></tr>
<tr><td>3 hour</td><td>4.97</td><td>3.91</td><td>2.30</td><td>2.79</td><td>1.307</td><td>0.20</td></tr>
<tr><td>4 hour</td><td>4.82</td><td>3.62</td><td>2.80</td><td>2.92</td><td>1.34</td><td>0.19</td></tr>
<tr><td>5 hour</td><td>4.42</td><td>3.35</td><td>2.47</td><td>2.83</td><td>1.28</td><td>0.21</td></tr>
<tr><td>6 hour</td><td>5.01</td><td>3.60</td><td>2.42</td><td>3.01</td><td>1.626</td><td>0.11</td></tr>
</table>
<u>Admission to hospital:</u>
9/22 patients in the ketorolac group were admitted to the hospital for continuation of therapy, while 10/19 visits by patients who received placebo resulted in hospital admission (p = 0.662)
<u>Rate of return to ED within 48 hours of discharge:</u>
Rates of return to the ED were similar for patients who received ketorolac (3/13) and for those in the placebo group (0/9, p = 0.358).
<u>Adverse events:</u>
One patient experienced local histamine response to morphine and was removed from the study. No other adverse effects were noted.
</td></tr>
<tr><td>Authors' conclusion</td><td>We were unable to demonstrate a synergistic analgesic effect for ketorolac in the treatment of pain from acute vaso-occlusive crisis in paediatric sickle cell disease.</td></tr>
<tr><td>Source of funding</td><td>Source of funding is not reported.</td></tr>
<tr><td>Comments</td><td>Patients were randomised in accordance with a computer generated randomisation schedule.</td></tr>
</table>

Table 49 Evidence table for Adawy et al (2005)

Bibliographic reference (Ref ID)	Adawy et al 2005 (Ref ID:5349)

Study type & aim	Controlled, randomised, double-blind study/ To study if the administration of ketorolac or methylprednisolone prior to morphine given by patient controlled analgesia (PCA) would reduce the dose requirement of morphine and attenuate morphine-related side effects or not.	
Number and characteristics of patients	Total: 45 children (group P = 15, group K = 15, group M = 15) Exclusions: Patients with known history of recurrent hospital admission for management of life-threatening complications, history of renal disease, peptic ulcer, bleeding disorder or use of analgesics or central nervous system active medications within 3 hours of enrolment. Patients who were readmitted to the ED within 48 hours of discharge due to recurrence of pain were excluded from the study. Inclusions: Children known to have SCD with painful episode and treated in the ED Patient characteristics: The three studied groups were comparable with regard to demographic data, age of first painful episodes necessitating admission, number of painful sites, number of ED visits in the last year and number of hospital admissions in the last year. Mean age (8.6 vs. 9.1 vs. 8.3), body weight (28.7vs. 29.6 vs. 30.3), gender (33% vs. 20% vs. 60% male) in groups P, K and M respectively did not significantly differ.	
Monitoring information and definitions	Nine faces pain scale (NFPS): pain assessment was started at the time of ED admission (before drugs were given, 0 time) and every 15 min in the first hour and then hourly till the end of the 6 hour observation period. NFPS is a set of 9 schematic faces depicting changes in the severity of expressed pain (0 = no pain/ very happy and 9 = severe pain/ very sad). Patients circled the face that represented how they felt. Adequate pain relief: Patient and caregiver recorded that pain was tolerable or completely resolved and no further IV analgesia was needed. Transfer to inpatient department: Patients who needed analgesia for more than 6 hours.	
Intervention	GROUP K: Drug: Ketorolac Dose: 1.0 mg/kg Route: Given over 30 minutes in 50 ml 0.9% saline solution Procedure: D5W in 0.45% saline was administered at a rate of one and half time the normal daily requirements. They were also given O_2 at a rate of 2 L/min via nasal cannula. Other pain relief: After finishing the study solutions, all patients received morphine sulfate via PCA pump and was prepared to deliver a demand dose of 1.0 ml (0.5 mg) with lockout interval of 10 minutes. Patients instructed for the use of PCA device. Patients with NFPC > 4/9 received rescue dose of double the demand dose, then resuming the standard regime.	GROUP M: Drug: Methylprednisolone Dose: 15 mg/kg Route: Given over 30 minutes in 50 ml 0.9% saline solution Procedure: as group K Other pain relief: as group K
Comparator	GROUP P: Drug: saline Dose: 50 ml of 0.9% saline solution over 30 minutes Route: as intervention group Procedure: as intervention groups	

<table>
<tr><td></td><td>Other pain relief: as intervention groups</td></tr>
<tr><td>Length of follow up</td><td>6 hours in the ED</td></tr>
<tr><td>Location</td><td>Egypt</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>
NFPS scores [Median (range)]:
<table>
<tr><th>Time</th><th>Group P, Placebo (n = 15)</th><th>Group K, Ketorolac (n = 15)</th><th>Group M, Methylprednisolone (n = 15)</th></tr>
<tr><td>Baseline</td><td>8 (6-8)</td><td>8 (7-8)</td><td>8 (7-8)</td></tr>
<tr><td>15 minutes</td><td>8 (5-7)</td><td>7 (6-7)</td><td>7 (6-7)</td></tr>
<tr><td>30 minutes</td><td>8 (5-7)</td><td>7 (5-6)</td><td>7 (5-6)</td></tr>
<tr><td>45 minutes</td><td>5 (5-6)*</td><td>4 (4-5)*†</td><td>4 (4-5)* †</td></tr>
<tr><td>1 hour</td><td>5 (4-6)*</td><td>4 (3-5)* †</td><td>4 (3-5)* †</td></tr>
<tr><td>2 hour</td><td>4.5 (3-5)*</td><td>3 (3-4)* †</td><td>3.5 (3-4)* †</td></tr>
<tr><td>3 hour</td><td>4 (3-5)*</td><td>3 (3-4)* †</td><td>3 (2-3)* †</td></tr>
<tr><td>4 hour</td><td>3.5 (3-4)*</td><td>2.5 (2-3)* †</td><td>2.5 (2-3)*</td></tr>
<tr><td>5 hour</td><td>3 (2-4)*</td><td>2 (2-3)* †</td><td>2 (2-3)*</td></tr>
<tr><td>6 hour</td><td>3 (2-3)*</td><td>2 (1-2)* †</td><td>2 (1-2)*</td></tr>
</table>
* P < 0.05 compared with baseline, † P < 0.05 compared with group P

Cumulative morphine requirements:
<table>
<tr><th>Time</th><th>Group P, Placebo (n = 15)</th><th>Group K, Ketorolac (n = 15)</th><th>Group M, Methylprednisolone (n = 15)</th></tr>
<tr><td>1 hour</td><td>2.35 (1.15)</td><td>1.95 (1.00)</td><td>2.05 (1.10)</td></tr>
<tr><td>2 hour</td><td>4.80 (1.85)</td><td>3.75 (1.35)</td><td>3.69 (1.50)</td></tr>
<tr><td>3 hour</td><td>7.40 (2.55)</td><td>5.30 (1.96)*</td><td>5.40 (1.75)*</td></tr>
<tr><td>4 hour</td><td>9.37 (3.13)</td><td>6.65 (2.05)*</td><td>7.10 (2.30)*</td></tr>
<tr><td>5 hour</td><td>10.40 (3.85)</td><td>7.33 (2.25)*</td><td>7.70 (2.65)*</td></tr>
<tr><td>6 hour</td><td>11.05 (4.10)</td><td>7.71 (2.70)*</td><td>8.10 (2.95)*</td></tr>
<tr><td>Rescue doses (mg)</td><td>2.70 (1.14)</td><td>1.60 (0.90)*</td><td>1.75 (0.95)*</td></tr>
</table>
*P < 0.05 compared with the control group

Adverse events:
<table>
<tr><th>Event</th><th>Group P, Placebo (n = 15)</th><th>Group K, Ketorolac (n = 15)</th><th>Group M, Methylprednisolone (n = 15)</th></tr>
</table>
</td></tr>
</table>

	Nausea	9	2*	2*
	Vomiting	7	1*	0*
	Respiratory depression	0	0	0
	Pruritus	2	2	0
	Patients needed ward admission	3	3	2
	Patients returned to the ED within 48 hours	0	0	0
	* P < 0.05 compared with the control group			
Authors' conclusion	Administration of ketorolac or methylprednisolone prior to morphine during the outpatient management of acute painful sickle cell crisis in children reduces cumulative morphine requirements and attenuates morphine-related nausea and vomiting.			
Source of funding	Sources of funding not reported.			
Comments	Patients were randomly assigned (computer generated random numbers sequence program).			

Table 50 Evidence table for Head et al (2010)

Bibliographic reference (Ref ID)	Head et al 2010 (Ref ID: 91)
Study type & aim	Double blind, randomised, placebo-controlled clinical trial/ To determine whether nitric oxide (NO) breathing reduces acute VOC pain in adult patients and to study the safety of NO.
Number and characteristics of patients	Total: 18 patients Exclusions: significant respiratory compromise, new focal neurological changes, acute priapism, known pregnancy or positive urine pregnancy test, other sickle haemoglobin variants, blood transfusion within 30 days, exposure to therapeutic NO, enrolment in other clinical trials, significant cardiac dysfunction, fever greater than 38.5 degrees, recent tobacco use, and chronic pain or treatment for VOC within the previous 12 hours. Inclusions: Patients with homozygous HbS experiencing uncomplicated severe acute VOC (score > 6cm on a VAS and total haemoglobin concentration > 6.0) were enrolled. Patient characteristics: Not reported

Monitoring information and definitions	Acute VOC: pain in the chest back, abdomen or extremities that could not be explained by any other complication of SCD or by any other cause other than SCD. Monitoring: Vital signs including blood pressure and oxygen saturation were monitored continuously during the 6 hour period and recorded at baseline and hourly before blood samples were taken. VAS: 0 for no pain and 10 for worst pain
Intervention	Drug: Nitric oxide Dose: 80 ppm with 21% final concentration of inspired oxygen. Route: inhaled (by facemask) Procedure: Patients meeting the eligibility criteria received standard ED treatment. IV catheter was placed to draw baseline blood samples and administer fluids and medications. After patients were stabilised, they were transferred to the clinical research centre where NO or placebo inhalation therapy was given by facemask. The study was administered for 4 hours, the patient was monitored for 2 additional hours after the study gas was stopped. Other pain relief: Pain medication consisted of IV morphine sulphate (initial dose up to 0.3 mg/kg body weight) and fluids (isotonic sodium chloride solution, 10 mL/kg over 30 minutes). A single dose of IV diphenhydramine (25-50 mg) was given to reduce narcotic side effects, if necessary. Additional IV morphine was delivered on demand by a patient controlled analgesia (PCA) device. Additional morphine was administered IV by PCA pump at a dose of 1-4 mg delivered on demand with a lockout period to prevent overdose. The study gas was given within 60 minutes after the initial IV morphine injection.
Comparator	Drug: Placebo (21% inspired oxygen) Dose: as above Route: as above Procedure: as above Other pain relief: as above
Length of follow up	6 hours
Location	USA
Outcomes measures and effect sizes	VAS pain scores: There was a decrease in pain score of 0.7 to 1.9 cm at each time point in the inhaled NO group as compared with decreases of 0.2 to 1.3 cm in the placebo group ($p = 0.002$). After 4 hours of NO treatment, the total reduction was 6.3 ± 2.2 cm in the INO group vs. 2.97 ± 2.1 cm in the placebo group ($p = 0.02$).
Authors' conclusion	This study fully supports the safety and efficacy in the use of NO gas in acute VOC.
Source of funding	Grant sponsor: INO therapeutics
Comments	Method of randomisation not reported and patient characteristics are not reported.

Table 51 Evidence table for Jacobson et al (1997)

Bibliographic reference (Ref ID)	Jacobson et al 1997 (Ref ID: 1852)
Study type & aim	Randomised controlled trial (RCT) to investigate the dose equivalence, clinical efficacy and safety of oral controlled-release morphine with continuous IV morphine in children admitted to hospital for severe episodes of sickle cell pain
Number and characteristics of patients	Total: 56 children enrolled (29 in IV treatment group) and 27 in oral treatment group). 50 patients were assessed for efficacy. Three patients receiving IV morphine and 3 patients receiving oral morphine were excluded from the efficacy analysis (one patient in each group was excluded for protocol violation, 2 patients were excluded in oral morphine for adverse events, one patient in oral morphine withdrew consent and two patients in oral morphine withdrew for inability to swallow). All patients were included in the safety analysis. Exclusions: Children with intractable nausea or vomiting and those who were unable to tolerate oral or intravenous morphine. Inclusions: Children aged 5-17 years with documented SCD who presented to the emergency department with painful episodes requiring admission to hospital and parenteral opioid therapy. A painful episode was defined as the occurrence of pain in the extremities, back, abdomen or chest that could only be explained by sickle cell disease. Patient characteristics: Patient characteristics were similar for both treatment groups. Mean age (IV=11.7 years, oral morphine= 10.7 years), mean number of painful sites (IV=2.5, oral morphine= 2.4), mean number of painful episodes in previous 12 months (IV=4.9, oral morphine= 5.0), mean number of painful episodes requiring admission in previous 12 months (IV=2.3, oral morphine=2.1) and mean loading dose (IV=0.12, oral morphine=0.13).
Monitoring information and definitions	Pre-Study: All patients had presented to the emergency department (ED) of the Hospital for Sick Children, Toronto. Pain scales: Faces pain scale (seven schematic faces that depict changes in expression of pain severity- from no pain to severe pain), Oucher scale, (six photographs of a child's face showing different expressions of pain positioned on a 0-100 vertical scale, positioned at 20-unit intervals), Children of eastern Ontario pain scale (CHEOPS, a behavioural observational scale showing six behaviours-crying, facial expression, verbal expression, torso position touch behaviour and leg position. These are observed at 5s and recorded in the following 25s, a five-point clinical pain assessment (none, mild moderate, severe, very severe) which was performed by a clinical investigator Other scales: Glasgow coma scale was used to assess degree of consciousness and was measured every 4 hours. Monitoring: Pain was assessed at 0900h, 1300h, 1500h, 2100h every day. Rescue analgesia was analysed by total number of doses per patient (every 24hours and use in six 4hour segments every 24 hours) Temperature, heart rate, respiratory rate and blood pressure were measured every 4hours Oxygen saturation and endtidal carbon dioxide were recorded 4times daily at the time of pain assessments. Chest involvement was documented by signs and symptoms of lower respiratory tract disease and evidence of new pulmonic infiltrate on chest radiography. Frequency of any other adverse events (not described below) was recorded daily using a non-directed questionnaire.

<table>
<tr><td>Intervention</td><td>Drug: Open-label (MS Contin; Purdue Frederick) controlled-release morphine tablets plus intravenous placebo (saline)
Dose and Timing: Loading dose of intravenous morphine of up to 0.15 mg/kg. Thereafter patients received 1.9 mg/kg controlled release morphine tablets or was administered every 12 hours
Route: IV route was not reported. Tablets were administered orally
Other pain relief: Breakthrough pain (exacerbation of pain that required short-acting, rescue analgesia) was managed with immediate-release oral morphine (0.4 mg/kg) as required every 2-3 hrs.
Paracetamol was only used to manage fever Children were not allowed to take any other opioid or non-opioid analgesic (other than those administered) during the study. Doses of oral morphine were increased simultaneously by about 30% every 12 hours in patients requiring 3 or more doses of rescue analgesia in a 24 hour period or for patients whose pain control was deemed to be inadequate. Doses of oral morphine were reduced by 30% in patients when effective analgesia (no pain or mild pain) was achieved and maintained for 12-24 hours.</td></tr>
<tr><td>Comparator</td><td>Drug: Continuous intravenous morphine plus placebo tablets
Dose and Timing: 0.04 mg/kg^{-1} h^{-1} continuous intravenous morphine administered every 12 hours
Route: IV route was not reported. Tablets were administered orally
Other pain relief: Breakthrough pain (as described in the intervention) was managed with intravenous morphine bolus (0.1mg/kg). Doses of intravenous morphine were increased simultaneously by about 30% every 12 hours in patients requiring 3 or more doses of rescue analgesia in a 24 hour period or for patients whose pain control was deemed to be inadequate. Doses were reduced by 30% in patients when effective analgesia (no pain or mild pain) was achieved and maintained for 12-24 hours.</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>Toronto Canada</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Table 1: Mean (SD) oral and parenteral morphine requirements
<table>
<tr><th></th><th>Intravenous Morphine</th><th>Oral Morphine</th></tr>
<tr><td>Morphine daily dose (mg)*</td><td>29 (15)</td><td>110 (52)</td></tr>
<tr><td>Daily dose range (mg)</td><td>7-96</td><td>20-300</td></tr>
<tr><td>Daily morphine dose by weight (mg/kg)</td><td>0.81 (0.30)</td><td>2.99 (0.75)</td></tr>
<tr><td>Daily rescue analgesia</td><td>0.21 (0.28)</td><td>0.33 (0.36)</td></tr>
<tr><td>Frequency of rescue analgesia (doses/day)</td><td>0.9 (0.7)</td><td>0.7 (0.8)</td></tr>
<tr><td>Duration of pain (days)**</td><td>5.4 (2.6)</td><td>4.2 (1.7)</td></tr>
</table>
*Oral to parenteral dose was assumed to be 4:1
** p = 0.0591
Table 1shows that mean morphine dose was similar for both treatment groups. Mean oral to parenteral dose ratio (3.7) was consistent with the target dose ration (4.0). There was no significant difference between the overall rates of rescue analgesia provided in each treatment group and the frequency of rescue analgesia was similar for both treatment groups</td></tr>
</table>

<table>
<tr><td></td><td>
Table 2: Differences in pain scores between treatment group
<table>
<tr><th>Pain scale</th><th colspan="2">Mean (SD) score</th><th rowspan="2">Difference (95% CI)</th><th rowspan="2">Significance (p)</th></tr>
<tr><td></td><td>Intravenous morphine</td><td>Oral morphine</td></tr>
<tr><td>CHEOPS</td><td>6.3 (1.5)</td><td>6.4 (1.4)</td><td>-0.7 to 0.5</td><td>0.8</td></tr>
<tr><td>Oucher</td><td>31.5 (25.4)</td><td>39.2 (21.7)</td><td>-16.2 to 0.9</td><td>0.3</td></tr>
<tr><td>Faces</td><td>2.2 (1.4)</td><td>2.4 (1.3)</td><td>-0.7 to 0.3</td><td>0.6</td></tr>
<tr><td>Clinical Assessment</td><td>1.7 (0.7)</td><td>1.9 (0.5)</td><td>-0.4 to 0.03</td><td>0.3</td></tr>
</table>
Table 2 shows there was no significant difference of pain score (for all pain scales) between the two treatment groups.
Other outcomes:
Additionally, there was no significant difference in overall scores for heart rate, blood pressure, temperature and the Glasgow coma scale between each treatment group nor was there a significant difference between the oxygen saturation and endtidal carbon dioxide when patients with evidence of chest involvement or chest crises were excluded from the analysis (oxygen saturation 96.8 vs. 97.3%, p = 0.6, endtidal carbon dioxide 38.0 vs. 37.2mm Hg, p = 0.7).
Analgesic use:
Frequency of rescue analgesia did not differ significantly between oral and intravenous morphine groups (0.7 [0.8] vs. 0.9 [0.7] daily doses, p=0.2. Frequency of opioid analgesia was required for a mean of 4.2 days (1.7) vs. 5.4 day (2.6), p = 0.0591.
Adverse events:
Common adverse events included fever, pruritus, nausea and/or vomiting and constipation. The frequency and severity of these events did not differ significantly between the treatment groups (62 vs. 52 reports, 16 vs.19 severe intensity events).
</td></tr>
<tr><td>Authors' conclusion</td><td>Oral controlled-release morphine is a safe and effective alternative to continuous intravenous morphine for managing severe pain episodes in children with sickle cell disease</td></tr>
<tr><td>Source of funding</td><td>Research grant from Purdue Frederick (MS Contin manufacturer)</td></tr>
<tr><td>Comments</td><td>Written informed consent was obtained from all patients, their parents or legal guardians (or both if appropriate). Patients were randomly assigned to either the oral morphine or intravenous morphine treatment groups (dosage and timing are as described as above). Randomisation was computer generated and done in blocks of 4 patients. Preparation and coding of active drugs was performed by the hospital pharmacy to ensure masking. The study code was kept in hospital pharmacy and only broken for patients who experienced serious adverse events. Infusions were identical in appearance and placebo was identical in appearance and taste to the active tablet. When oral therapy was given doses were rounded to the nearest available strength (5mg, 15mg, 30mg, 60mg or 100mg).</td></tr>
</table>

Table 52 Evidence table for Gladwin et al (2011)

Bibliographic reference (Ref ID)	Gladwin et al 2011 ((Ref ID: 36)
Study type & aim	Prospective multi-centre double-blind randomised controlled, phase 2 study to evaluate the efficacy of inhaled nitric oxide and to determine whether inhaled nitric oxide can reduce the duration of painful crises in SCD
Number and characteristics of patients	Total: 1078 participants aged 10 years and over with known SCD were assessed for eligibility identified during presentation for VOC at the ED. Presenting at 11 centres. Exclusions: Patients with sickle cell haemoglobin C disease, exposure to therapeutic nitric oxide in previous 12 hours, use of phosphodiesterase-5 inhibitors, L-arginine nitroprusside or nitroglycerine within the previous 12 hours, treatment for VOC at an ED or other clinic in the previous 48 hours, hospitalisation within the previous 14 days of presentation, more than 10 previous hospitalisations for VOC in the preceding year, clinical diagnosis of bacterial infection at presentation, current enrolment in other studies (except hydroxyurea studies), pregnancy or breast-feeding, chronic transfusion or exchange transfusion in the preceding 30 days, suspected splenic sequestration, new pulmonary infiltrate at presentation, prior participation in the study. 920 patients were excluded: 710 patients did not meet study criteria, 81 refused to participate, 137 did not participate for other reasons. Inclusions: Patients with known SCD (10 years and over) recruited by presentation at the ED or in the outpatient setting while in pain. Patient characteristics: 150 participants in total (75 in each arm) 37male, 38 female, median age 22.9 (in nitric oxide arm), 38 male, 37 female, median age 24.5 (in placebo arm) Four patients withdrew from each group but all 150 participants were evaluated by intention to treat
Monitoring information and definitions	Pre-Study: no pre-study monitoring was recorded Pain scales: Pain was measured using a 0-10point scale along a 10cm horizontal line (1 point=1cm, visual analogue scale (VAS). No pain=0, Worst pain=10. Participants indicated their intensity of pain by making a mark along the line. This was measured at baseline and at hours 2, 4, 6 and 8 and every 4 hours thereafter. The score was the measure (in cms to the nearest 0.1cms) Primary efficacy variable: Time to VOC resolution (which was defined by freedom from parenteral opioid use for at least 5 hours). VAS scores showing ≤ 6cm which was maintained for at least 2 readings, 2 hours apart and each at least 3 hours apart since the last dose of parenteral opioids; the patients' ability to walk (except chronic nonambulatory patients); agreement of the patient, parent or guardian and physician that residual pain was low enough to be managed at home. Data was censored at the actual time of discharge from hospital, for patients who were discharged with missing end-point data. Death before discharge in patients that did not meet VOC resolution was censored at a time later than the latest time of censoring. Duration of VOC was determined by length of crisis in any patients that were hospitalised for more than 30 days without VOC resolution. Secondary efficacy variable: Was length of admission to discharge, VAS score over time, total dose of opioids in first 8 hours after enrolment and during admission, rate of ACS or pneumonia needing blood transfusion, proportion discharged in first 24 hours, proportion returning to ED or hospital within 30 days, change in nitrate/nitrate levels and methamaglobate levels as measures of nitric oxide and metabolisms and reactions in the blood. Secondary evaluation of pain relapse was determined by the proportion of participants that were treated again for pain in a hospital, ED or other unit within 24 hours and within 30 days of discharge. Safety monitoring: Methemoglobin values were monitored at baseline and every 2 hours for the first 8 hours and every 24 hours for the remainder of the study. If values reached 5% or more, then the treatment dose was decreased by 50%. Therapy was discontinued for any value greater than 7.5%. Therapy was also stopped if the physician, investigator or patient deemed it to be necessary; for any serious adverse events; and patients showing clinically significant hypotension, sepsis or septic shock, or sustained pulse oxygen level below 85% for more than 15 minutes while receiving

<table>
<tr><td></td><td>supplemental oxygen</td></tr>
<tr><td>Intervention</td><td>Drug: Inhaled nitric oxide
Dose: 80ppm for 4 hours and then 40ppm for 4 hours. Any participant that remained in hospital for longer than 8 hours received study gas administered through a pulsed flow delivery. The dose was 6mL/pulse/breath for participants with a body weight of ≥ 27kg or 3mL/pulse/breath if less than 27kg for a maximum period of up to 72 hours
Route: Initial dose was treated via face mask, additional treatment of pulsed flow gas was treated via nasal cannulae
Procedure: Nitric oxide gas cylinders were assigned. Nitric oxide was delivered with air mixed with oxygen to achieve a constant fraction of inspired oxygen (FIO_2) of 24%</td></tr>
<tr><td>Comparator</td><td>Drug: Placebo study gas was 100% grade 5 nitrogen gas
Dose: As in intervention
Route: As in intervention
Procedure: Placebo gas cylinders were assigned. Placebo gas was delivered with air mixed with oxygen to achieve a constant fraction of inspired oxygen (FIO_2) of 24%</td></tr>
<tr><td>Length of follow up</td><td>Only analysis time of up to 72 hours was reported other follow up was not specified</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Efficacy of inhaled nitric oxide gas vs. placebo gas on VOC:
There was no significant difference in VOC resolution according to treatment type (p = 0.87, estimated median time to resolution= 73.0hrs, 95% CI =46.0 to 91.0 for inhaled nitric oxide group and 65.5 hours 95% CI = 48.1 to 84.0, for placebo group).
Table 1: Effect of inhaled nitric oxide on secondary outcomes
<table>
<tr><th>Secondary outcome</th><th>Inhaled Nitric oxide
(n = 75)</th><th>Placebo
(n = 75)</th><th>P-value[a]</th></tr>
<tr><td>Length of hospitalisation in days, median (IQR),</td><td>4.1 (2.0 to 6.0)</td><td>3.1 (1.7 to 6.4)</td><td>.30</td></tr>
<tr><td>VAS score at 24h, mean (95%CI), cm</td><td>6.1 (5.3 to 6.8)</td><td>6.0 (5.4 to 6.6)</td><td>.90</td></tr>
<tr><td>VAS score change from baseline, mean (95%CI), cm
At 2h
At 4h
At 6h
At 8h</td><td>
-0.4 (-0.8 to -0.1)
-0.6 (-1.2 to -0.1)
-1.2(-1.7 to -0.7)
-1.3 (-1.8 to -0.8)</td><td>
-0.7 (-1.1 to -0.3)
-0.8 (-1.3 to -0.3)
-1.1 (-1.6 to -0.6)
-1.2 (-1.8 to-0.7)</td><td>.90</td></tr>
<tr><td>Opioids in first 8h, median (IQR) mg/kg</td><td>0.28 (0.09 to 0.54)</td><td>0.23 (0.07 to 0.70)</td><td>.74</td></tr>
<tr><td>Total opioids, median, (IQR), mg/kg</td><td>2.8 (1.4 to 6.1)</td><td>2.9 (1.1 to 9.9)</td><td>.73</td></tr>
</table></td></tr>
</table>

ACS requiring transfusion, No (%), [95%CI]b	8 (10.7) [4.7 to19.9]	7 (9.3) [3.8 to 18.3]	.79
Discharged within 24h, No (%), [95%CI]	5 (6.7) [2.2 to 14.9]	7 (9.3) [3.8 to 18.3]	.55
Returned to ED within 30d, No (%), [95%CI]	8 (10.8) [4.8 to 20.2]	11 (15.1) [7.8 to 25.4]	.44
Re-hospitalised within 30d, No (%), [95%CI]	9 (12.2) [5.7 to 21.8]	17 (23.0) [14.0 to 34.2]	.08
Methemoglobin, mean, (95%CI), %			
At 0h	0.73 (0.59 to 0.86)	0.81 (18.0 to 32.9)	
At 4h	2.29 (2.05 to 2.52)	0.82 (0.66 to 0.98)	<.001
At 24h	1.32 ((1.07 to 1.57)	0.88 (0.71 to 1.06)	
Plasma nitrate, mean (95%CI) µmol/Lc			
At 0d	24.5 (18.3 to 32.6)	24.3 (18.0 to 32.9)	
At 2d	60.9 (48.5 to 76.3)	22.2 (16.01 to 30.5)	.03
At 4d	36.2 (22.3 to 58.8)	20.9 (13.8 to 31.8)	
Plasma nitrite, mean (95%CI) µmol/L			
At 0d	0.22 (0.18 to 0.26)	0.21 (0.18 to 0.24)	
At 2d	0.30 (0.25 to 0.36)	0.24 (0.19 to 0.30)	.77
At 4d	0.23 (0.16 to 0.34)	0.27 (0.22 to 0.32)	
Whole blood nitrite, mean (95%CI) µmol/L			
At 0d	0.28 (01.4 to 0.56)	0.23 (0.14 to 0.37)	
At 2d	0.40 (0.24 to 0.67)	0.27 (0.17 to 0.41)	.31
At 4d	0.45 (0.23 to 0.85)	0.37 (0.22 to 0.62)	

[a] From Wilcoxon 2-sample test for comparison of medians; unpaired *t*- test for comparison of means at specified time points; Pearson χ^2 test for comparison of proportions; and repeated measures ANOVA for comparison of means over time
[b] Clopper-Pearson (exact) 95% confidence limits

Table 1 shows that the secondary analysis did not differ significantly according to treatment type (including median length of hospitalisation, in mean VAS score at 24 hours and mean decreases in VAS score changes up to 8 hours, percentage of patients discharged in 24hrs, percentage of patients who returned to ED in 30 days and percentage of patients re-hospitalised in 30 days.

Decreases in mean VAS scores at 2 hour intervals over 8 hours of treatment did not differ by treatment group. Reductions in pain score ranged from 0.4cm, (95%CI= 0.1-0.8) to 1.3, (95% CI = 0.8-1.8) in nitric oxide group vs. reductions from 0.7cm (95%CI =0.3-1.1) to 1.2cm (95%CI= 0.7-1.8) in the placebo group (*p*=.0.90*)*

In addition cumulative opioid use up to 72 hours after initial presentation yielded no effect of inhaled nitric oxide vs. placebo (0.33 mg/kg: IQR 0.2-0.7, vs. 0.33 mg/kg, IQR 0.1-0.6, over 4 hours, *p*=.47;0.57 mg/kg; IQR 0.2-0.9 over 8 hours, *p*=.19 and 0.78mg/kg; IQR 0.3-1 over 12 hours, *p*=.35).

	Table 2: Participants with serious adverse events {No, (%) [95%CI]}[a] {No, (%) [95%CI]}[a] **System Organ Class** / **Preferred Term** / **Inhaled Nitric Oxide (n=75)** / **Placebo (n=75)** Blood and lymphatic system disorders / Acute chest syndrome / 5 (6.7) [2.2 to 14.9] / 5 (6.7) [2.2 to 14.9] Gastrointestinal disorders / Dysphagia / 1 (1.3) [0.03 to 7.2] / 0 (0.0) [0.00 to 4.98] General disorders and administration site conditions / Pyrexia / 1 (1.3) [0.03 to 7.2] / 1 (1.3) [0.03 to 7.2] Sensation of foreign body / 1 (1.3) [0.03 to 7.2] / 0 (0.0) [0.00 to 4.98] Investigations / Haemoglobin decreased / 1 (1.3) [0.03 to 7.2] / 0 (0.0) [0.00 to 4.98] [a] Clopper-Pearson (exact) 95% confidence limits Table 2 shows there was no difference in treatment groups for the percentage of participants who developed ACS as a serious adverse event
Authors' conclusion	Inhaled nitric oxide had no effect on the primary outcome of time to VOC resolution or on the secondary analyses (including length of hospitalisation, change in VAS scores and total opioid use. In conclusion the results indicate that inhaled nitric oxide does not reduce VOC severity in SCD
Source of funding	Collaboratively supported by Ikaria and Intramural Research Division of NHLBI, NIH, US Department of Health and Human Services
Comments	Participants were randomised using block randomisation by site and age at entry (10-15 years and >15 years) in blocks of 4 (1:1 randomisation). Coded labels were applied to both study gas and nitric oxide cylinders at the manufacturers' site. A blinded (blanked out) version of the face mask nitric oxide delivery system covered nitric oxide and nitrogen dioxide monitor and displays. Placebo was administered in the same way to ensure double blinding of both participants and investigators.

Table 53 Evidence table for Weiner et al (2003)

Bibliographic reference (Ref ID)	Weiner et al (Ref ID: 5730)
Study type & aim	Prospective double blind, randomised placebo-controlled trial (RCT) to examine the efficacy and safety of inhaled nitric oxide (INO) for treatment of VOC in paediatric patients with SCD
Number and characteristics of patients	Total: Paediatric patients with SCD who were experiencing uncomplicated severe acute VOC (score of > 6cm on a 10cm VAS were recruited Exclusions: ED treatment for VOC within the previous 24 hours; VOC concomitant with other acute processes (including Acute chest syndrome and potential serious infection amongst others); transfusion or use of investigational drugs other than hydroxyurea within last 30 days; allergy to morphine; smoking more than ½ pack per day pregnancy.

	Inclusions: 79 Paediatric patients aged 10-21 with sickle cell anaemia (HbSS) (haemoglobin SC (HbSC)or (HbS-β- thalassemia (Hbs-βthal) were assessed for eligibility. Patient characteristics: 25 patients aged 10-21 years with SCD and severe VOC were randomised to treatment (only 20 patients were included in analysis; 10 in each arm). Nitric oxide group (male= 6, mean age 17.6, SD= 2.4). In placebo group (male=5, mean age 15.2, SD=2.6)
Monitoring information and definitions	Pre-Study: After completion of ED patients received standard treatment with morphine (0.1mg/kg –up to a maximum of 6mg) and fluids (isotonic sodium chloride solution- 1mL/kg) over 30 minutes Pain scales: The primary pain assessment tool was a 10cm VAS 0= no pain, 10=worst pain Other monitoring tests: Blood pressure determination, oxygen saturation (measured by pulse oximetry) and lab studies were performed immediately prior to inhalation and every hour during the 4 hours of inhalation and continued to be monitored every hour for 2 hours after therapy ceased Outcome measures: The primary outcome measure was change in pain score at 4hrs Secondary outcomes included amount of parenteral narcotic used at 4, 6 and 24 hours after initiating inhalation. Narcotic use at 4 and 6hrs was calculated as mg/kg of morphine, over 24 hours it was calculated as morphine equivalents using the standard conversion of 1mg fentanyl =10mg morphine. This is because patients could change to alternative narcotics after 6 hrs. Safety measures included minimum systolic blood pressure; minimum SPO_2; maximum concentration of delivered NO_2 and maximum concentration of methemoglobin. Other outcome measure was length of hospitalisation
Intervention	Drug: Nitric Oxide -780ppm in nitrogen was mixed with oxygen to deliver INO (with 21% final concentration of inspired oxygen), plus morphine Dose: INO = 80ppm, morphine= 0.025 mg/kg per dose with a 7 min lock out and a 0.3 mg/kg 4hr cumulative dose lock out Route: Face mask for INA and PCA pump for morphine Procedure: Both INO and morphine were administered simultaneously within 90min of initial ED morphine dose (see pre-study monitoring information for this dose). Inhalation continued for 4 hrs. The mask was removed for 5mins every hour of inhalation. This was for patient needs immediately after pain assessment; vital signs and laboratory studies were obtained at this time. Other medications: Morphine with diphenhydramine for pruritus and ondansetron for nausea were the only other medications allowed during the 6hr observation period.
Comparator	Drug: Placebo inhalation therapy (with 21 %inspired oxygen) plus morphine Dose: As intervention Route: As intervention Procedure: As intervention
Length of follow up	Patients were enrolled over a 24 month period. Other follow-up details were not reported
Location	USA
Outcomes measures and effect sizes	Primary endpoint: Decrease in pain scores between groups at 4 hours was greater in the INO group than placebo group but this was not statistically significant (2.0cm vs. 1.2cm, p = 0.37). Repeated measures ANOVA showed the VAS pain score significantly decreased in the INO group at 1.0cm more each hour

<table>
<tr><td></td><td>than placebo group (p = 0.02). Two hours after inhalation completion (at 6-hrs) the mean VAS scores in the placebo group remained unchanged from that at 4hrs, but the INO the mean VAS score had increased and was similar to the score in the placebo group
<u>Secondary outcomes:</u>
The INO group used statistically less parenteral morphine over the 6hr period than placebo group (mean cumulative morphine use = 0.29 vs. 0.44 mg/kg, p = 0.03). Over the 4 hour inhalation period and over the 24 hour assessment period the amount used was lower in the INO group but this was not statistically significant (0.26 vs. 0.32 mg/kg over 4 hours, p = 0.21 and 0.63 vs. 0.91 mg/kg, p = 0.15). There was a trend towards shorter duration of hospitalisation in patients in the INO group compared to placebo group but this was not significant (median=78 vs. 100 hours, p = 0.19).

Table 1 shows there were no episodes of hypotension, clinically significant SPO_2, toxic concentrations of NO_2 or clinically significant increases in methemoglobin.
<u>Table 1: Safety outcomes</u>
<table>
<tr><th>Outcome Measures</th><th>INO Group (n=10)</th><th>Placebo group (n=10)</th></tr>
<tr><td>Systolic blood pressure (6h) Mm Hg
Lowest mean (SD)</td><td>92
113 (19)</td><td>97
113 (10)</td></tr>
<tr><td>Oxygen saturation (4h) %
Lowest mean (SD)</td><td>90
96.4 (2.6)</td><td>94
97.1 (2.1)</td></tr>
<tr><td>Nitrogen Dioxide delivered (4h) ppm
Highest mean (SD)</td><td>2.3
1.1 (0.6)</td><td>0
0</td></tr>
<tr><td>Methemoglobin (4h) %
Highest mean (SD)</td><td>2.7
1.4 (0.7)</td><td>0.8
0.5 (0.2)</td></tr>
</table></td></tr>
<tr><td>Authors' conclusion</td><td>Nitric oxide (INO) may be beneficial for acute VOC- but as this was a pilot study, the preliminary results need to be further investigated.</td></tr>
<tr><td>Source of funding</td><td>Study supported by a US Food and Drug Administration Orphan Products Development Grant</td></tr>
<tr><td>Comments</td><td>Participants were randomised to treatment group (method of randomisation and blinding not reported). Patients or families (depending on age) who met eligibility criteria provided written informed consent</td></tr>
</table>

Table 54 Evidence table for Grisham & Vichinsky (1996)

Bibliographic reference (Ref ID)	Grisham & Vichinsky 1996 (Ref ID:6582)

Study type & aim	A prospective double blind crossover trial to evaluate the comparative safety and efficacy of Ketorolac tromethamine (KT) and Meperidine (MP) in children and adolescents with Sickle cell anaemia (SCA).
Number and characteristics of patients	Total: 20 patients seen in at the ED. All patients were in VOC and were enrolled on a convenience basis Exclusions: Exclusions on age and presence of restrictive airways disease, hepatic, renal or bleeding disorders, allergies to NSAI agents Inclusions: Children aged 10 years and over with SCA, seen at the ED with VOC were eligible Patient characteristics: 20 patients enrolled in the study. 5 patients were enrolled on two separate occasions but were entered as separate participants because each of their pain episodes was unrelated. Patients were aged 11-19 years, (mean age 14) 11 patients (55%) were male, and the frequency of pain in various anatomical regions was variable. Pain had been present in most patients for 24 hours or less.
Monitoring information and definitions	Pre-Study: Patients had a complete history and physical examination- standard management was administered if appropriate. Routine lab studies, cardio-respiratory and oxygen saturation monitoring were undertaken. Patients had an intravenous line placed and hydration at a minimum of 1.5 times maintenance requirements, No oral analgesic medications were provided. Pain scales: Visual Analogue Scale- a horizontal scale (presented on a ruler) ranging from 'no pain' to 'the worst pain I've ever had'. Patients' marked a point across the scale to identify their current pain intensity level. Categorical scale- showing five categories of pain intensity (no pain, slight pain, mild pain, moderate pain, strong pain). Patients circled the category which best described the pain intensity they were currently experiencing. Facial Affective scale- Depicting 9 pictorial representations of facial expressions (from very happy to very sad). Patients had to identify the emotion which best described the way they were feeling. Other scales: Sedation scale- a 7 point scale ranging from 0=Wide awake; 1= Drowsy, but not sleeping; 2=Sleeping intermittently; 3= Sleeping constantly awakes with verbal stimulation; 4= Sleeping constantly arouses to tactile stimulation and stays awake >1minute; 5= Sleeping constantly arouses to tactile stimulation and stays awake <1minute; 6= Sleeping constantly, unarousable. Monitoring: Baseline measures of pain scales and sedation scale were taken for all patients by the current attending physician before the initial analgesic dose was administered. These scales were then recorded at 30 min intervals for first phase (lasting approx. 21/2 hours (a further 120 min in first treatment phase and 150 min in second phase). 6 Patients experiencing total pain relief were excluded from second phase. Data analysis was performed both with (during first treatment phase) and without these high responders (in the second treatment phase). Patients with adverse events were recorded also. At the end of treatment patients were asked to identify which treatment they thought was MP and also which treatment they preferred (either first or second treatment). Mean values of pain scores and other measures were assessed using repeated measures ANOVA
S of the scale Intervention	Drug: KT Dose: Parenteral dose 1.0 mg/kg Route: Intra-muscular route used for first 8 patients, thereafter, all subsequent patients were given drugs intravenously
Comparator	Drug: MP Dose: Parenteral dose1.5 mg/kg Route: See above (in intervention)
Length of follow	Patients were enrolled on a convenience basis over an 18 month period.

up	
Location	USA
Outcomes measures and effect sizes	Phase one pain scores: Mean VAS score was 73. Patients receiving KT had significantly larger decreases in VAS pain scores over 150 min observation period (*F* within participants = 10.59, p < 0.001). The greatest decrease in pain scores occurred in first 30 min after administration of both drugs (significantly less pain was reported in the KT group (at 30 min mean VAS = 39 after KT and 54 after MP, P < 0.001). After an initial decrease in VAS at 30 min, patients receiving MP showed a small, persistent increase in VAS (mean VAS at 120 min = 57). At 150 min patients receiving KT were still reporting significantly less pain than MP patients (VAS scores = 36 vs. 56, p < 0.001). Similar differences were found between the KT and MP groups when the 6 patients reaching full pain relief were excluded. There were no statistical differences between the two groups over the 150 min observation. At 30 min after initial drug administration VAS scores were 63 for KT/MP and 66 for MP/KT. There was a continued decrease in VAS after the 30 min measure in patients that had received KT. Phase two pain scores: Mean baseline VAS before second drug administration was 53 (for patients receiving KT first) and 65 (for patients initially receiving MP). There was no significant difference in VAS over the 150 minutes between KT and MP. Mean VAS score 30 mins after second analgesic dose was 54, 36 for MP/KT and 36 for KT/MP. The largest reduction in VAS occurred in first 30 minutes. Mean VAS at 120 minutes was 38 after MP and 54 after KT. There was no significant difference in VAS scores of either group after 150 minutes (mean VAS = 38 in KT/MP and 51 in MP/KT) Complications and sedation scores: There were significantly more complications after patients received MP than after KT (85% of patients had no complications after KT, 63% had no side effects after MP, p < 0.001). One patient scored a 5 after MP and the overall trend was towards a consistently higher sedation score (more sleepy) after MP. There was a statistically significant difference in sedation scores between KT and MP over 120 minutes observation period (*F* within participants = 3.12, p < 0.05) Miscellaneous data: 13 participants that completed both phases reported the preference of narcotic. There was no significant difference between the participants who preferred KT (n=6, 46%) over MP (n=7,54%)
Authors' conclusion	Parenteral KT is a useful analgesic for acute management of pain in older children with sickle cell disease. When compared to MP KT is an effective and safe analgesic for VOC in children.
Source of funding	Supported in part by a grant from National Institutes of Health
Comments	Patient or parent provided written informed consent for patient (depending on age). Patients were randomly assigned (method of randomisation not reported) to one of two treatment phases. One half of patients received KT then MP and the other half vice versa. Patient, physician and family were blinded to order of drug administration. Nurse providing care was un-blinded- All medication was given in standard volume in an unmarked syringe. Treatment in each phase was monitored for two and a half hours.

Table 55 Evidence table for Robieux et al (1992)

Bibliographic reference (Ref ID)	Robieux et al 1992 (Ref ID: 2305)
Study type & aim	Prospective, double- blind randomised controlled trial (RCT). The study was designed as a prospective (before and after) evaluation of two different analgesic regimes. The study had three aims: To compare the efficacy and safety of a continuous infusion (CIV) of morphine and intermittent parenteral opioids (IPO) in children with sickle cell disease; to determine whether 50% oxygen administration can reduce the duration of severe pain in patients receiving CIV morphine; and to measure morphine concentration at a steady state for pharmacokinetic and pharmacodynamics analysis in patients receiving CIV morphine.
Number and characteristics of patients	Total: 66 children with sickle cell disease (SCD) who were admitted to the hospital for severe VOC requiring parenteral opioid therapy. 32 patients were studied in Phase 1 and 34 were studied in Phase 2. Exclusions: Patients with clinical and radiological signs of chest crisis; O2 saturation lower than 92% Inclusions: Children aged 3-18 years with SCD admitted to the hospital (for the reasons defined above) Patient characteristics: Participants in both groups were similar in respect to age and body weight. Phase 1 (n=32,3-17 years, mean age 10.7 ± 3.9 years, body weight 14 to 70 kg, mean 30.0 ± 12.2kg). Phase 2 ~(n=34, 3-18 years, mean age 10.8 ± 4.9 years, body weight 15 to 72 kg, mean 32.0 ± 14.9kg).
Monitoring information and definitions	Pre-Study: Routine management of a VOC included rehydration with intravenous fluids and continuation of penicillin v prophylaxis. This was provided in addition to provision of analgesia. In febrile patients a blood culture was drawn, acetaminophen was given and penicillin was replaced with intravenous cefuroxime. Colace was given to prevent opioid-induced constipation. In phase 2 transcutaneous O2 saturation was measured on admission Pain scales: A Behavioural Pain Score (BPS) was used to assess severity of pain by behavioural observation. Scores ranged from 0 (no pain) to 10 (maximum pain) A BPS of equal to or greater than 6 indicated moderate to severe pain. Any score of 5 or less was considered to reflect effective analgesia. BPS scores were assessed every 8 hrs. Other scales: Glasgow Coma Scale (GCS) was performed every 4 hrs. Vital signs were recorded every 2 hrs. Total body clearance of morphine: Morphine clearance (TBC) was calculated using the following formula: Steady state was achieved for any given rate of infusion (K) when two consecutive concentrations were less than 10% different. Concentration at steady state (CSS) calculated as the mean of these concentrations. TBC was calculated as K divided by CSS. Monitoring assessments: Neurological monitoring included a measurement of papillary diameter and was recorded every 4 hrs. Adverse effects of opioids: included nausea, vomiting sweating and pruritus and was recorded every 8 hours; Opioid toxicity was defined by the presence of any 2 of the following: drowsiness or coma; pinpoint pupils; emesis; sweating or pruritus; or respiratory rate <12/min. Opioid dose was decreased or stopped in such cases. Oxygen therapy and respiratory monitoring: were assessed and a chest x-ray was performed when clinically indicated. For patients in phase 2 transcutaneous oxygen-saturation (O2 sat), was measured on admission, every 8 hours for the first 24 hours and every morning thereafter. For patients wearing an oxygen mask O2 sat was measured after the mask had been taken off and patients had been breathing room air for10 minutes; determination of morphine concentrations was identified in patients receiving morphine, by blood samples that were drawn every morning, and when morphine toxicity was observed.

<table>
<tr><td>Intervention</td><td>Drug: O2 therapy or standard care
Dose: various concentrations and flow rates (not specified)
Route: not reported but assumed to be as in comparator
Procedure: 16 patients received O2 therapy for at least a day, the remaining 16 did not receive O2.
Other pain relief: Standard opioid analgesic regimes were provided: Opioid amounts were standardised to equivalent doses of parenteral morphine (included 1:1 for morphine, 1:7.5 for meperidine and 1:10 for codeine) via intramuscular or intravenous bolus every 3 or 4 hours</td></tr>
<tr><td>Comparator</td><td>Drug: O2 therapy or room air
Dose: 50% O2
Route: via a venturi face mask
Procedure: Patients were randomised to receive either room air (n=11), or 50% O2 (n=14). Compliance was encouraged by nurses and patients were checked every 2 hours
Other pain relief: All patients received CIV of morphine according to the following protocol: A loading dose of 0.15 mg/kg of morphine sulphate followed by CIV of morphine at an initial rate of 0.04 mg/kg/hr (40µg/kg/hr). Doses were increased where necessary, in (0.02mg/kg/hr (20 µg/kg/hr) units every 8 hours, up to a maximum of 1mg/kg/hr (100 µg/kg/hr). CIV morphine was decreased or stopped in serious adverse events</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Table 1 below shows the mean dose of opioids was similar between the two groups. There was no difference in duration of hospital stay or opioid therapy between the two groups. The number of hours where children experienced moderate or severe pain was significantly lower in phase 2 compared to phase 1($p < 0.05$)
Table 1: Mean opioid dose and duration of pain, opioid therapy and hospital stay in groups 1 and 2
<table>
<tr><th>Factor Tested</th><th>Group 1 (n=32)
Mean± SD</th><th>Group 2 (n=34)
Mean ±SD</th><th>P value</th></tr>
<tr><td>Morphine-equivalent dose (µg/kg/hr).</td><td>32 ± 20</td><td>34 ± 11</td><td>NS</td></tr>
<tr><td>Duration of hospital stay (days))</td><td>6.9± 2.5</td><td>7.1 ± 4</td><td>NS</td></tr>
<tr><td>Duration of opioid treatment (days</td><td>5.1± 2.4</td><td>4.7 ± 2.8</td><td>NS</td></tr>
<tr><td>Duration of severe pain (days)</td><td>2.0 ±1.8</td><td>0.9 ± 1.0</td><td><0.05</td></tr>
</table>
In phase 2 the duration of pain was similar in patients receiving 50% O2 compared with patients receiving 21% O2 (0.94 ±1.08 and 0.95 ± 1.19 days, NS). Oxygen did not shorten the duration of severe pain compared to placebo group (0.94± 1.08 and 0.95 ± 1.19 days). No severe opioid toxicity was observed in either group. Frequency of adverse events is shown in Table 2. The only significant difference was found in drowsiness which was more frequent in patients in phase 2.

Table 2: Frequency of opioid side effects in group 1 and group 2
<table>
<tr><th>Side Effect</th><th>Group 1 (n=32)</th><th>Group 2 (n=34)</th><th>p Value</th></tr>
<tr><td>Pruritus</td><td>9 (28%)</td><td>5 (15%)</td><td>NS</td></tr>
<tr><td>Sweating</td><td>9 (28%)</td><td>12 (34%)</td><td>NS</td></tr>
<tr><td>Nausea</td><td>4 (12.5%)</td><td>9 (26%)</td><td>NS</td></tr>
</table></td></tr>
</table>

	<table><tr><td>Emesis</td><td>8 (25%)</td><td>4 (11%)</td><td>NS</td></tr><tr><td>Drowsiness</td><td>13 (41%)</td><td>25 (74%)</td><td>0.05</td></tr><tr><td>Bradypnea</td><td>2 (6%)</td><td>3 (9%)</td><td>NS</td></tr></table> Morphine TBC was calculated in 24 children in phase 2. Table 3 shows that TBC was greater in children before puberty than after (40.4 ± 10 vs. 28 ± 11 mL/kg/min, p<0.05). Table 3: Age-dependent Total Body Clearance of morphine in children <table><tr><th>Age</th><th>Number of patients</th><th>TBC (ml/kg/min)</th></tr><tr><td>Pre puberty</td><td>11</td><td>40.4 ± 10</td></tr><tr><td>During puberty</td><td>5</td><td>37.1 ± 9</td></tr><tr><td>Post puberty</td><td>8</td><td>28.0 ± 11*</td></tr><tr><td>Total</td><td>24</td><td>± 11.3</td></tr></table>*p < 0.05 (ANOVA)
Authors' conclusion	In children with severe VOC continuous infusion of morphine provides better analgesia than intermittent opioid therapy. 50% oxygen therapy had no effect on the duration of pain.
Source of funding	Study sponsored by Physician Services Incorporation Foundation and supported by Foundation of Medical Research, Paris
Comments	Parents provided written informed consent for any child under 16 years of age, otherwise patients provided this directly. Patients in phase 2 were randomised to treatment (see comparator). Double blind randomisation was used (details were not specified)

Table 56 Evidence table for Zipursky et al (1992)

Bibliographic reference (Ref ID)	Zipursky et al 1992 (Ref ID:2327)
Study type & aim	A randomised blinded study to assess the efficacy of oxygen inhalation therapy on the number of irreversibly sickled cells (ISC) and reversibly sickled cells(RSC) – therefore the effect of oxygen therapy on the prevention and reversal of erythrocyte sickling in patients with SCD in vaso-occlusive crisis. The study attempted to identify whether oxygen inhalation therapy can reduce the number of sickled cells in patients that are in and out of crisis; and would the reduction in the number of circulating cells reduce the duration, severity and progression of VOC.
Number and characteristics of patients	Total: Both patients attending the clinic who were currently experiencing a crisis (n=23) and patients attending the clinic with SCD but who were not in crisis were examined in two phases to the study. Exclusions: Patients with clinical or radiologic signs of chest crisis (in crisis sample) Inclusions: Participants in the 'not in crisis' sample included patients with homozygous haemoglobin SS disease who were clinically stable. Participants in the 'in crisis' sample included 23 patients with acute painful VOC admitted to the hospital. Five participants in this sample were studied twice and therefore the total sample of participants included in this group was 28. Patient characteristics: Participants 'not in crisis' were aged 4-17.5 years (mean age =12, SD±4.6). Participants 'in crisis' were 23 children aged 3-18 years (mean age 10.7, SD 4.8). Data analysis was carried out on only 25 participants in crisis (due to sickle counts only being available for these

<table>
<tr><td></td><td>participants)</td></tr>
<tr><td>Monitoring information and definitions</td><td>Pre-Study: Patients with a VOC were treated using continuous IV morphine for control of pain and hydration and parenteral antibiotics were provided if clinically indicated. A blood culture was drawn, aceteaminophen was given and penicillin was replaced by IV cefuroxime in febrile patients. Patients remained in a hospital bed throughout the study
Pain scales: Severity of pain for patients in crisis was assessed using the Behavioural Pain Score (BPS) every 8 hrs. A score of 6 or more indicated moderate to severe pain. At the start of testing all children had reported a score >6.
Face mask compliance: Compliance was measured using a 5-point scale: 1= If the mask was correctly placed 0-24% of the time; 2= correctly placed 25-49% of the time; 3= correctly placed 50-74%; 4=correctly placed 75-99% and 5= correctly placed 100% of the time it was used. A score of 4 or 5 was considered to show patient compliance, and a score of ≤3 was considered to show non-compliance. Nurses monitored patient compliance every 2 hours
Other monitoring assessments: Transcutaneous oxygen saturation was measured on admission and every 8 hours for the first 24 hours and daily thereafter. Oxygen saturation (O2 sat) was monitored in patients receiving oxygen after their mask had been removed for 10 minutes. Venous samples were taken thirty min prior to oxygen administration and 30 min later (immediately prior to oxygen inhalation was started) Repeat venous samples were drawn after 5 and 2tion. A 0 min of oxygen administration. Blood samples were also taken 5 and 30 min after the oxygen was discontinued
Outcome definitions: Within 1 min of collection of the blood samples 50 µl of blood were added to two tubes placed in separate buffers for 15 min. One sample contained a buffer containing dissolved oxygen- and this was deemed sufficient to reverse all reversibly sickled cells (RSC). This value was used in analysis. Duration of crisis was monitored by length of hospitalisation, opioid therapy and measuring the hourly dose of morphine.</td></tr>
<tr><td>Intervention (patients not in crisis)</td><td>Drug: Oxygen
Dose: Initial dose was 50% Oxygen-gas mix for 20 min duration. Six patients were also given an additional 28% oxygen immediately following initial dose
Route: Venturi valve oxygen mas
Other pain relief: not reported</td></tr>
<tr><td>Comparator (patients in crisis- with VOC)</td><td>Drug: Oxygen (n=15) or room air (n=10)
Dose: 50% mix of oxygen-gas
Route: As intervention
Other pain relief: not reported</td></tr>
<tr><td>Length of follow up</td><td>Not reported</td></tr>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures and effect sizes</td><td>Studies of patients in VOC
There was a significant difference in mean RSC value/100 between participants receiving 50 %O2 and those receiving room air (mean ± SEM= 8.1 ± 3 vs. 18.5 ± 4.2, p<0.05). The ISC values did not differ significantly in those receiving oxygen or room air (6.25 ± 1.7 vs. 7.4 ± 1.5). Table 1 shows there was no significant difference in duration of hospitalisation, opioid therapy, severe pain or mean hourly dose of morphine between patients receiving O2 therapy or room air. Four patients receiving O2 therapy produced a sustained reduction of RSC (reaching 0 in all cases), but the results indicate that the reduction of RSCs did not have a significant change on the duration of crisis.
Table 1: Duration of sickle cell crisis
<table>
<tr><th></th><th>Air</th><th>Oxygen</th><th>Selected[a]</th></tr>
</table>
</td></tr>
</table>

	(10)	(15)	(4)
Hospitalisation (days)	5.4 ± 2.6	6.7 ± 3.6	6.5 ± 3
Opioid therapy (days)	3.9 ± 2.3	4.7 ± 1.9	5 ± 2.7
Severe pain[b] (days)	0.94 ±1.08	0.95 ± 1.19	1.4 ± 1.2
Mean hourly dose of morphine (µg/k/h)	40 ± 15	48 ± 29	64 ± 74

[a] 4 participants treated with O2 that showed the most profound and sustained reduction in RSC
[b] Based on pain score >5

Table 2 shows that crisis does appear to be associated with a reduction in the number of RSCs in the blood. The samples taken in patients in crisis was significantly lower than those taken in patients that were not in crisis ISC values showed a small but non-significant change.

Table 2: Reversibly (RSC) and irreversibly (ISC) sickled cells before and after onset of sickle cell crisis

	Sickled cells (mean ± SEM)	
	RSC	**ISC**
Pre crisis (11)	29.5 ± 7.1	11.7 ± 2.8
Crisis (11)	9.3 ± 2	7.2 ± 2.1

RSC pre-crisis/ crisis p =0.013 ISC pre-crisis/ crisis p= 0.074

Table 3 shows that haemoglobin levels fell in the O2 group but not in the air group. The difference was borderline significant ($p < 0.06$). Reticulocyte counts fell significantly in both groups ($p < 0.03$) but the difference between groups was not significant.

Table 3: The effect of oxygen therapy on haemoglobin and reticulocyte values

	Admission	**Discharge**
Haemoglobin (g/L)		
Air (11)	83 ± 4.25 a	84 ± 2.7
Oxygen (17)	97 ± 1.7	87 ± 1.9
Reticulocytes (109/L)		
Air (11)	540 ± 82	409 ± 60
Oxygen (17)	502 ± 38	384 ± 42

Authors' conclusion	Oxygen therapy can reduce the number of circulating sickle cells, but the results from this study suggest, that O2 therapy does not appear to influence the duration of crisis
Source of funding	Sponsored by Physicians Services Inc.
Comments	Written consent was provided by parents or children directly (if older than 16 years). Patients that were not in crisis were not randomised to treatment (receiving only 50% oxygen- with 6 participants receiving an additional 28% oxygen). Patients in crisis were chosen at random (method used not reported) to receive either room air or 50% oxygen. A head-delivery system was designed to allow the double-blind administration of oxygen or room air through a Venturi face mask. compliance to the mask was encouraged by nurses and monitored every 2 hours

Review question 2: Non-pharmacological management

Table 57 Evidence table for Wang et al (1988)

Bibliographic reference (Ref ID)	Wang et al 1988 (Ref ID:2622)
Study type & aim	Double-blind, randomised, cross-over study/ To compare transcutaneous electrical nerve stimulation (TENS) versus placebo in sickle cell crisis
Number and characteristics of patients	Total: 22 patients Exclusions: No details are reported Inclusions: No details are reported Patient characteristics: 20 patients had HbSS, 1 had HbSC and 1 had $HbTh^0$ and had an age range 12-27 years (median 17.5 years). There were 12 females. Two crises were evaluated in some patients. For the second crisis of the same severity, the patient was crossed over to receive the opposite of the initial treatment (treated as independent observations in the analysis).
Monitoring information and definitions	Severity of pain: reported by the patient on a scale from 0-10 (with 10 being the severest pain the patient had ever experienced). Grading of severity of pain: Patient was assigned to the highest severity grade in which at least 1 criterion was satisfied. GRADE I: mild pain, pain rating 1-4. Complete or substantial relief from last dose of oral non-narcotic analgesia (e.g. acetaminophen, aspirin). Hospitalisation not necessary. GRADE II: moderate pain, pain scale rating 5-7. Complete or substantial relief from last dose of oral narcotic analgesia (e.g. acetaminophen with codeine, meperidine). Hospitalisation not necessary. GRADE III: severe pain, pain rating scale 8-10. Complete or substantial relief from last dose of parenteral narcotic analgesia. Hospitalisation not necessary. GRADE IV: same pain scale rating as grade III, but little or no relief from the last dose of parenteral narcotic analgesia. Hospitalisation necessary. Patient evaluation: After 4 hours, patients were asked to assess whether the treatment had been helpful, not helpful or harmful in its overall effect.
Intervention	TENS: battery powered 100 dual channel TENS apparatus was used. This unit generates square wave electrical impulses and has adjustable settings for pulse rate and width as well as a separate pulse amplitude controls. In this study, the pulse rate was set at approximately 100 Hz (pulses per second) and the pulse width at 30μs. These are settings within recommended ranges.

	Procedure: TENS electrodes were applied according to applied principles. Within each painful area, a painful locus (area of maximal sensitivity) was palpated and the distal electrode applied. If no pain locus could be identified, the electrode was placed over a trigger point in the involved area as indicated on the reference map of pain pathways. The location of the proximal electrode varied. If the pain was confined to an extremity or small area, the electrode was placed over a trigger point or along a pain pathway within the involved dermatome. If the pain involved the back, chest or abdomen, the electrode was placed over the paravertebral dorsal nerve root corresponding to the pain dermatone(s). After placement of the electrodes, the pulse amplitude was slowly increased, which caused the patient to experience an initial tingling sensation and then mild discomfort. The amplitude was then reduced until the sensation was comfortable again. The unit was turned off prior to randomisation. Intervention: If the patient were assigned to TENS, the assistant reset the amplitude settings on the TENS device to their original levels.
Comparator	TENS: as above Procedure: application of TENS as above Placebo: If the patient was assigned to placebo, the assistant left the amplitude settings at zero.
Length of follow up	Trial encouraged for at least 4 hours
Location	USA
Outcomes measures and effect sizes	Pain ratings: There were no significant differences in improved pain ratings at 1 hour in the TENS and placebo group respectively, (12/27 [44%] vs. 10/32 [31%], χ^2 = 1.09, p = 0.30). There were also no significant differences at 4 hours (13/25 [52%] vs. 14/30 [47%], χ^2 =0.16, p = 0.69). Use of analgesia: The two groups were similar in terms of analgesic use. 12 patients (20%) required narcotic analgesics before the 1 hour rating with no significant difference between placebo (25%) and TENS (14%, χ^2 = 1.07, p = 0.30). 38 patients (63%) required pain medication before the 4 hour rating, again with no significant difference between placebo (66%) and TENS (61%, χ^2 =0.16, p = 0.69). Patient evaluation: A significant difference in the patient's assessment of the overall value of TENS and placebo treatment was found. In 17/23 trials with TENS (74%) patients felt the treatment had been helpful, in 5 trials (22%) it was neither helpful nor harmful and in 1 trial (4%) it was thought harmful. Of the 28 placebo trials, 11 (39%) were felt to be helpful, 15 (54%) were neither helpful nor harmful and 2 (9%) were judged harmful. There were significantly more 'helpful' evaluations in the TENS group when compared to the placebo group (χ^2 = 6.11, p = 0.01)
Authors' conclusion	No substantial benefit from TENS could be demonstrated by pain ratings or measurement of analgesic use in patients experiencing sickle cell crises. However, about three quarters of patients subjectively felt that TENS was helpful.
Source of funding	This work was supported by the American-Lebanese-Syrian Associated Charities (ALSAC).
Comments	If patients had pain in multiple sites, a separate pain rating was determined for each area. The site of most severe pain was used in the analysis. Randomisation was carried out by an assistant using randomisation cards for each severity grade. The assistant also covered the machine's indicator light and controls with tape so that the patient and investigators remained unaware of the assignment.

Review question 3: Clinical signs and symptoms of acute complications

Table 58 Evidence table for Kopecky et al (2004)

Bibliographic reference (Ref ID)	Kopecky et al 2004 (Ref ID: 1119)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a post hoc analysis of an RCT comparing oral with continuous infusion of morphine. Aim: To assess exposure to morphine as an etiologic factor for acute chest syndrome (ACS) in sickle cell disease (SCD)
Number and characteristics of patients	Total: 50 patients (26 in the continuous infusion group and 24 in the oral morphine group). 16 patients developed ACS at some time during their admission (12/21 in oral morphine group and 4/23 in continuous infusion group with complete data). At enrolment 4 patients were diagnosed with ACS and were excluded. Inclusion: Children with SCD aged between 5 and 17 years, who were seen in the emergency department with severe sickle cell pain and who required at least 2.5 mg of intravenous (IV) morphine or at least 10 mg of oral morphine per day were enrolled into the study Exclusion: No specific exclusion criteria was reported Patient characteristics: There were 9 males and 15 females with a mean age of 10.7 ± 3.7 years in the oral morphine group and 13 males and 13 females with a mean age of 11.7 ± 3.4 years in the continuous infusion group. The two groups did not differ clinically at the time of entering the trial. On admission, there were no significant differences in the physiologic characteristics (weight, heart rate, respiration rate and blood pressure) between patients in either of the two groups. The ages of the children in whom ACS subsequently developed were not significantly different between treatment groups. On admission to hospital, there were also no significant differences in the physiologic characteristics and the number of painful sites between the patients in whom ACS later developed and those in whom ACS did not develop regardless of the treatment group.
Definitions	Acute Chest Syndrome (ACS): this was defined a priori as the presence of new chest radiograph changes from the time of admission (appearance of pleural effusion or infiltrates), the need for supplemental oxygen therapy (increasing fractional inspiratory oxygen requirements to maintain oxygen saturation), and the presence of clinical findings such as such as fever or cough, decreased air entry, audible chest finding on auscultation and elevated white blood cell count. *Note:* The diagnosis of ACS was established by the clinician caring for the children, who were blinded to the study medications. These values were repeatedly assessed in each patient by blinded observers. Although ACS was defined a priori, rates of ACS were not originally compared between the two study groups, because ACS has been widely believed to be a feature of SCD in general. The possibility that it is associated with or induced by morphine was not originally entertained.
Prognostic factors and confounders	Clinical variables: oxygen saturation, heart rate, respiration rate (in oral vs. IV morphine exposure) Laboratory variables: end-tidal carbon dioxide (in oral vs. IV morphine exposure) Outcome of interest: development of ACS (in oral vs. IV morphine exposure) Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	During hospitalisation (patients seen in emergency department)

<table>
<tr><td>Location</td><td>Canada</td></tr>
<tr><td>Outcomes measures</td><td>Parameters assessed for the incidence of ACS exacerbation (compared between treatment groups by Student t test)
Oxygen saturation
Heart rate
End-tidal carbon dioxide
Respiratory rate</td></tr>
<tr><td>Results</td><td>Note: limited details of pharmacokinetic analyses are reported in this evidence table
<u>Clinical and laboratory data by ACS across treatments (mean ± SD)</u>
<table>
<tr><td></td><td colspan="2">Oral morphine</td><td colspan="2">Continuous infusion morphine</td></tr>
<tr><td>Parameter</td><td>ACS (n = 12)</td><td>No ACS (n = 9)</td><td>ACS (n = 4)</td><td>No ACS (n = 19)</td></tr>
<tr><td>Oxygen saturation (%)</td><td>90.9 ± 5.4*</td><td>96.8 ± 2.9</td><td>94.5 ± 3.6</td><td>97.3 ± 2.0</td></tr>
<tr><td>Heart rate (beats/min)</td><td>108.6 ± 15.0*</td><td>94.4 ± 16.0</td><td>103.8 ± 20.2</td><td>97.0 ± 13.7</td></tr>
<tr><td>End-tidal carbon dioxide (mm Hg)</td><td>38.0 ± 2.9</td><td>39.4 ± 5.4</td><td>37.2 ± 1.1</td><td>38.3 ± 5.1</td></tr>
<tr><td>Respiration rate (breaths/min)</td><td>29.3 ± 2.7*</td><td>24.0 ± 4.9</td><td>28.5 ± 8.0</td><td>24.7 ± 8.9</td></tr>
</table>
* Oral group oxygen saturation, p = 0.01; oral group heart rate, p = 0.05; oral group respiration rate, p = 0.01. All other between treatment and between group comparisons, P > 0.05.

Of patients who received oral morphine, 12 (57%) had ACS at some time during their admission, a finding 3-fold greater than among those children who received continuous infusion morphine (4/23, 17%, p < 0.001). The table above shows that children who received oral morphine and in whom ACS developed showed significant differences in oxygen saturation, respiratory rate and heart rate compared with children in whom ACS did not develop or who received continuous infusion morphine.
<u>Pharmacokinetics of morphine:</u>
<table>
<tr><td>Parameter</td><td>Oral morphine (n = 4)</td><td>CIV morphine (n = 11)</td></tr>
<tr><td>Dose ($mg.kg^{-1}.d^{-1}$)</td><td>4.2 ± 1.0</td><td>0.76 ± 0.21</td></tr>
<tr><td>Mean AUC_{0-12} (ng.h/mL)</td><td>614.3 ± 322.9*</td><td>157.00 ± 77.9</td></tr>
<tr><td>Mean C_{max} (ng/mL)</td><td>97.0 ± 62.6*</td><td>21.7 ± 12.2</td></tr>
<tr><td>Mean C_{min} (ng/mL)</td><td>29.7 ± 16.8 **</td><td>8.8 ± 4.6</td></tr>
<tr><td>Mean $t_{max(0-12)}$ (h)</td><td>2.5 ± 2.5</td><td>5.6 ± 4.85</td></tr>
<tr><td>Mean apparent clearance (L/min)</td><td>3.0 ± 1.0</td><td>1.6 ± 0.7</td></tr>
<tr><td colspan="3">Values are mean ± SD. Except where shown, all comparisons between oral and CIV morphine for morphine were not statistically</td></tr>
</table></td></tr>
</table>

	significant. AUC_{0-12} area under concentration time curve from 0 to 12 hours; C_{max} maximum plasma concentration, C_{min} minimum plasma concentration; $t_{max(0-12)}$ time to C_{max} from 0 to 12 hours. * p = 0.001, ** p = 0.002 The AUCs of morphine and morphine-6-glucuronide (M6G) were significantly higher in orally treated patients that in those treated with infusion. In the subgroup studied kinetically, 3 children receiving oral morphine and 1 receiving IV morphine had development of ACS. The mean AUC of morphine in these children tended to be higher (396 ± 393 ng.h/mL) than in those without development of ACS (221 ± 172 ng.h/mL). A similar trend was seen for M6G. Given the small number of ACS cases, this comparison does not have meaningful power.
Authors' conclusion	In conclusion, there appears to be an association between systemic exposure to morphine and development of ACS. At this time there is no data on rates of ACS in children not receiving opioids, because it is ethically impossible not to treat pain. However, the introduction of novel parenteral nonsteroidal anti-inflammatory drugs may allow the rates of ACS in children not receiving opioids to be examined in the future.
Source of funding	Supported by a grant from Purdue Pharma, Pickering, Ontario, Canada
Comments	Morphine exposure may have been within toxic range for the sustained-release oral formulation group (Patients received IV loading dose of morphine sulfate, 0.15 mg/kg, followed by an initial morphine infusion of at least 0.04 mg . kg^{-1}. h^{-1} until the start of the study. Children randomised to the continuous infusion group then received ≥ 0.04 mg. kg^{-1}. h^{-1} and oral placebo and those randomised to the oral morphine group received ≥ 1.9 mg. kg^{-1}. h^{-1} and continuous IV placebo within 24 hours of presentation to the emergency department). For each patient undergoing pharmacokinetic analysis, plasma morphine and M6G concentrations were plotted against time and the maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to C_{max} (t_{max}), area under the concentration time curve (AUC) at steady state AUC_{ss} and clearance rate (morphine only) were calculated from the individual plasma concentration-time profiles.

Table 59 Evidence table for Finkelstein et al (2007)

Bibliographic reference (Ref ID)	Finkelstein et al 2007 (Ref ID: 544)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a retrospective, self-matched, case-crossover design Aim: To explore the potential association between a dose-response effect of morphine exposure and the development of ACS in children with SCD who present with vaso-occlusive crisis (VOC)
Number and characteristics of patients	Total: Data from 17 children were included in the study (920 hospitalisations of children with SCD for painful VOC were identified, data from 866 hospitalisations were excluded where ACS did not develop, 34 hospitalisations in which patients had respiratory symptoms or radiographic abnormalities on presentation and 3 patients who did not suitable reference hospitalisations without ACS) Inclusion: All children (aged < 18 years) with SCD who presented to the emergency department for painful VOC between April 1st 2000 and March 31st, 2006. Exclusion: Patients who presented to the hospital with clinical or radiographic manifestations compatible with pneumonia or a possible diagnosis of ACS (e.g. pulmonary infiltrates on chest radiograph) prior to receiving opioid therapy were excluded, as were data from patients who did not develop ACS. Patient characteristics: There were 13 girls and 4 boys with index hospitalisations who had a mean age 8.9 (SD 4.0) years and a mean weight 30.9 (SD 15.2) kg. The mean age of the reference hospitalisation was 8.6 (SD 3.4) years with a mean weight 27.3 (SD 11.2) kg. Most patients (n = 14) were HbSS while two patients had HbS/β-thalassemia and one patients had HbSD. There were no significant differences in patient characteristics (age, weight,

	temperature, heart rate, respiration rate, oxygen saturation, haemoglobin, white blood cell count, platelets and cumulative dose of morphine) between index and reference hospitalisations. As expected, mean index hospitalisations were significantly longer than reference hospitalisations (8.0 vs. 6.2 days, p = 0.03)
Definitions	Morphine treatment: at this institution, morphine is administered as a continuous drip, with a typical initial rate of 10 µg/kg per hour. Dose escalation and the need for additional rescue doses are determined following assessment of patient response. Index hospitalisation: a hospitalisation during which ACS developed (defined for each patient). During the index hospitalisation, the time (in hours) from initiation of IV morphine infusion to the development of ACS (index interval) was identified. Reference hospitalisation: a hospitalisation in which ACS did not develop (defined for each patient). When multiple admissions could serve as potential reference hospitalisations for a given patient, the most approximate admission to the index admission was used. A comparison time interval during the reference hospitalisation (reference interval), at which time ACS did not develop was defined. This interval began with the initiation of IV morphine infusion and was of the same duration as the index interval. ACS: defined 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 as interpreted by a paediatric radiologist.
Prognostic factors and confounders	Clinical variables: morphine exposure Laboratory variables: none reported Outcome of interest: development of ACS Confounders: Because oral codeine (a prodrug of morphine) is occasionally used to treat VOC, the authors added 10%[20] of the total codeine dose to the cumulative morphine dose in the instances in which it was given (n = 3).
Length of follow up	During hospitalisation (6 year study period)
Location	Canada (patients presenting to the emergency department at The Hospital for Sick Children, Toronto)
Outcomes measures	Morphine exposure-the cumulative dose of morphine for each patient's index and reference hospitalisations were compared using the paired t test and the normal distribution of the data for index and reference hospitalisations were confirmed using the Shapiro-Wilks W test. The mean infusion rates in the index admissions versus those in the reference admissions were examined, and the total cumulative dose of morphine received by patients throughout their entire reference hospitalisation was quantified.
Results	Efficacy The mean (SD) cumulative dose of morphine during the index interval was 1.24 (SD 0.60) and 1.44 (SD 0.84) mg/kg during the reference interval. The mean (SD) morphine infusion rate was 28.6 (10.0) µg/kg per hour during index hospitalisations as compared with 31.4 (12.8) µg/kg per hour during reference hospitalisations, and the mean (SD) total cumulative morphine dose throughout all reference hospitalisations was 3.3 (1.8) mg/kg. The mean cumulative morphine dose and infusion rates were found to be higher during hospitalisations in which ACS did not develop, suggesting no dose-effect relationship.
Authors' conclusion	Among these children with SCD who presented with VOC, the administration of morphine was not found to be associated with a dose-response effect on the risk for ACS
Source of funding	None reported

Comments	For each patient's index and reference intervals, the cumulative dose of morphine administered, route of administration, and infusion rates were determined by a detailed review of the nursing notes in each patient's charts. The paper charts of each patient were independently reviewed by three paediatricians and researchers. None of the researchers who extracted data from hospital records were directly involved in the acute care of any patients in the study. Used fixed dose protocol so risk for under or over dosing with morphine may have been reduced.

Table 60 Evidence table for Buchanan et al (2005)

Bibliographic reference (Ref ID)	Buchanan et al 2005 (Ref ID: 914)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a retrospective chart review Aim: To evaluate the development of ACS in patients with SCD admitted for VOC and treated with either morphine sulfate or nalbuphine hydrochloride. Paper also aims to assess efficacy in pain relief between the different analgesics by comparing the number of days of inpatient hospitalisation as a proxy for pain control (results not shown in this evidence table).
Number and characteristics of patients	Total: 175 patient admissions (89 treated with morphine sulfate and 86 treated with nalbuphine hydrochloride). There were a total of 37 (27%) episodes of ACS (26 in morphine group and 11 in Nubain group, including patients who changed medication). Patient receiving Nubain on admission had more medication changes during the hospital stay (12% vs. 3%, p = 0.04). Of the 86 Nubain patients, 10 patients had a change of medication and 8 of these were changed to morphine. Of the 89 morphine patients, 3 changed medications, 1 of these was changed to Nubain. Of the patients that did not change medication, 6/76 developed ACS in the Nubain group and 25/86 developed ACS in the morphine group. Inclusion: patients with an admitted diagnosis of sickle cell vaso-occlusive crisis who were between the age of 5 and 19 years. Exclusion: patients were excluded if they were transferred from another hospital for continued care, were readmitted within 4 weeks after treatment for ACS on the previous admission, had a positive chest x-ray on admission, were on chronic red cell transfusions, had other underlying diseases which would confound the primary outcome such as severe hepatic dysfunction, were on daily opioid therapy at home, had neurological symptoms suggesting a transient ischemic event (TIA) or an acute stroke (CVA), were unable to grade their level of pain due to intellectual or physical limitations, were not admitted for a sickle cell pain event or were not treated with one the study medications. Patient characteristics: There was no significant difference found in demographic or pre-admission history (age, gender, phenotype, previous history of ACS, or hospitalisation rate within the preceding 12 months), no admission vital signs or haemoglobin levels between the two treatment groups. The mean age was 11 years in the morphine group, 49% were male and 58% with SS phenotype. The mean age in the Nubain group was 11 years, 48% were male and 60% with SS phenotype. There was no statistical difference in complaint of chest pain in the morphine group (20) compared with the Nubain group (21, p > 0.05). Accompanying fever (≥ 38.4°C) was more common in the patients who received Nubain but this difference was not statistically significant. Patients receiving morphine on admission were more likely to have higher white cell counts on admission (15.2 vs. 13.5 10^3/L, p < 0.05) and to use CIV for medication administration (49% vs. 3%, p < 0.001). They also had longer hospital stays than patients who received nalbuphine (median stay 3 vs. 4 days, p < 0.001). Although the mean presenting pulse oximetry was not significantly different, more patients receiving Nalbuphine had pulse oximetry levels less than 95% (12 vs. 26, p < 0.05). In this study population, 65% had previous ACS events and of these 19% acquired new pulmonary infiltrates during the review. For comparison of patients with and without ACS unadjusted analyses indicated that age (p < 0.001), admitting haemoglobin (p < 0.0001), white cell count

<table>
<tr><td></td><td>(p < 0.0001), level of pain (p < 0.0001), administration of morphine (p < 0.01) and use of continuous infusion (p < 0.005) were all statistically significant.</td></tr>
<tr><td>Definitions</td><td>ACS: a new pulmonary infiltrate on chest radiograph after admission and before discharge. This information was recorded in the medical notes but if the chest x-ray report was not available in the chart, radiology records were reviewed for confirmation. All chest x-rays were reviewed and the final report signed by an attending radiologist.

Note: The use of continuous infusion accompanied by PCA was the choice of the admitting team although nubain is less frequently prescribed via continuous infusion in this institution. In general, when continuous infusion (CIV) of morphine is prescribed the accompanying orders include standardised calculations for patients administered medication (PCA)</td></tr>
<tr><td>Prognostic factors and confounders</td><td>Clinical variables: Morphine, PCA, pain score, age, chest pain, SS vs. other phenotype, pulse oximetry < 95%
Laboratory variables: Haemoglobin, white blood cell count (WBC)
Outcome of interest: development of ACS
Confounders: CIV is completely confounded with morphine use (50% in morphine group vs. 3% in Nubain group, p = 0.0001). There were also 14% with missing pain scores. Pain scores are strongly associated with ACS so used two types of analyses: used only cases with pain scores and imputed pain scores based on associated factors. Because of the strong confounding, multivariate models that use either morphine or CIV are presented as well as a model with both included.</td></tr>
<tr><td>Length of follow up</td><td>During hospitalisation (study period between January 1999 and December 2002)</td></tr>
<tr><td>Location</td><td>USA (in three children’s hospitals in Atlanta)</td></tr>
<tr><td>Outcomes measures</td><td>Morphine, PCA, pain score, age, chest pain, SS vs. other phenotype, pulse oximetry < 95%, Haemoglobin, white blood cell count (WBC)-see various multivariate models for results</td></tr>
<tr><td>Results</td><td>Results of logistic regression analysis of ACS predictors:
<table>
<tr><td></td><td></td><td colspan="3">Complete cases (N = 146)</td><td colspan="3">Imputed pain scores (N = 171)</td></tr>
<tr><td>Predictor variable</td><td>Unadjusted OR (95% CI)</td><td>Morphine</td><td>PCA</td><td>Morphine + PCA</td><td>Morphine</td><td>PCA</td><td>Morphine + PCA</td></tr>
<tr><td>Morphine</td><td>2.8 (1.28, 6.14)</td><td>2.96 (0.84, 10.50)</td><td>-</td><td>2.06 (0.47, 8.9)</td><td>2.73 (0.98, 7.6)</td><td>-</td><td>1.85 (0.57, 6.04)</td></tr>
<tr><td>PCA</td><td>3.56 (1.66, 7.64)</td><td>-</td><td>2.99 (0.88, 10.15)</td><td>2.04 (0.49, 8.47)</td><td>-</td><td>3.18 (1.11, 9.08)</td><td>2.29 (0.68, 7.65)</td></tr>
<tr><td>Pain score (range 1-10)</td><td>1.6 (1.22, 2.21)</td><td>2.14 (1.36, 3.37)</td><td>1.98 (1.28, 3.06)</td><td>2.06 (1.30, 3.27)</td><td>1.95 (1.34, 2.84)</td><td>1.81 (1.24, 2.63)</td><td>1.86 (1.26, 2.72)</td></tr>
<tr><td>Hgb (gm/dl)</td><td>0.6 (0.46, 0.78)</td><td>0.60 (0.41, 0.87)</td><td>0.58 (0.40, 0.85)</td><td>0.58 (0.40, 0.85)</td><td>0.66 (0.49, 0.90)</td><td>0.65 (0.47, 0.88)</td><td>0.65 (0.47, 0.89)</td></tr>
<tr><td>WBC (103/L)</td><td>1.22 (1.13, 1.32)</td><td>1.25 (1.11, 1.41)</td><td>1.24 (1.11, 1.41)</td><td>1.25 (1.11, 1.41)</td><td>1.21 (1.10, 1.34)</td><td>1.21 (1.10, 1.34)</td><td>1.22 (1.10, 1.34)</td></tr>
</table></td></tr>
</table>

	Age (years)	0.85 (0.77, 0.95)	0.88 (0.77, 1.01)	0.87 (0.76, 1.01)	0.87 (0.76, 1.01)	0.87 (0.77, 0.98)	0.87 (0.77, 0.99)	0.87 (0.77, 0.99)
	Pulse oximetry < 95	1.13 (0.46, 2.76)	-	-	-	-	-	-
	Chest pain	0.87 (0.37, 2.1)	-	-	-	-	-	-
	SS versus other	1.81 (0.81, 3.97)	-	-	-	-	-	-

Unadjusted analyses represent separate analyses of each individual predictor unadjusted for any other predictor. Both complete case and imputed score analyses are multivariate analyses with OR's adjusted for all other factors with an OR shown. Separate models that used only morphine or PCA or both are listed. Complete cases indicate models that used patients with no missing data for the factors used in the model. Imputed pain score models used pain scores imputed for cases of missing values.

The table above summarises the estimated OR's for the various analyses. The first set of OR's are unadjusted estimates for the risk of the development of ACS and show that morphine, use of CIV, increased pain scores, elevated white cell count, lower haemoglobin level and younger age are significantly related to increased risk of ACS. Models using complete cases (leaving out missing scores) and those using imputed pain scores are also presented. Results are relatively consistent across the models. Individually, morphine and CIV show similar risk and when combined both risks reduce indicating some substitution effect. In the imputed pain model both morphine (p = 0.054) and CIV (p = 0.03) show evidence of an effect.

<u>Exploratory analyses:</u>

Two exploratory analyses were carried out. If the patients that indicated a change in medication during hospitalisation were excluded (n = 13, 3 morphine, 10 Nubain), a stronger association of ACS with both morphine (OR = 5.9, CI 1.5, 27.8) and CIV (OR = 6.8, CI 1.86, 25.2) in the imputed pain models and the same substitution effect when using both morphine (OR = 3.8, CI 0.86, 16.8) and CIV (OR = 3.8, CI 0.86, 16.8) in the model. It was also noted that there were particular Hgb and WBC cut-offs for which there were no cases of ACS. If we restrict analyses to patients with Hgb ≤ 10.5 and WBC ≥ 9 we get similar results for morphine (OR 2.7) and CIV risk (OR = 3.3).

Authors' conclusion	Although the study did demonstrate a strong association in the development of ACS with morphine, it was confounded with the presence of CIV.
Source of funding	None reported
Comments	The data abstraction tool was validated for accuracy and inter-rater reliability using 25 patient records. The authors estimated a Kappa statistic = 1 (perfect agreement in all cases) for agreement of the primary outcome of ACS. For vital signs (temperature, pulse oximetry, pain and respiratory rate) gave K ≥ 0.69 for all measures. Only one admission per patient was accepted for review to prevent bias from patients who suffer frequent ACS events. Patients were assigned to a medication group (morphine or nubain) based on first medication delivered once hospitalised. Although documentation of the total amount of the medication received by the patient was desired, variability in charting provided inaccurate data in this uncontrolled review. Three hospitals in Atlanta were chosen to acquire a broad assessment of socioeconomic differences, experiences of physicians and nursing staff involved in the care of these patients. Bronchodilator therapy by pressured nebulisation is administered to patients who have had a history of ACS or known to have

	asthma when that are admitted for VOC. Study was set in three hospitals: one tertiary hospital staffed by an attending haematologist and mid-level practitioners with no involvement of paediatric residents or fellows, one tertiary hospital with a well-defined area for haematology/oncology inpatient care in close proximity to the outpatient haematology/oncology services and one tertiary hospital accommodating two medical schools and associated with a tertiary care county hospital. Patients are under the direct supervision of a general paediatric attending with a senior paediatric resident and first year residents. The haematology team consults on all patients with SCD on admission and follows them daily.

Table 61 Evidence table for Styles et al (2000)

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Styles et al 2000 (Ref ID: 1545)</td></tr>
<tr><td>Type of prognostic study & aim</td><td>Study type: Prognostic factor/ explanatory study using a prospective cohort study
Aim: To determine the accuracy of secretory phospholipase A_2 ($sPLA_2$) in predicting ACS in hospitalised patients with VOC.</td></tr>
<tr><td>Number and characteristics of patients</td><td>Total: 14 patients during 21 hospital admissions for VOC
Inclusion: Only patients with VOC and without ACS at the time of admission were eligible for the study.
Exclusion: no specific exclusion criteria reported
Patient characteristics: 13 patients had HbSS and 1 patient had HbSβ-thalassemia. The average age of the patients was 12.6 ± 4.9 years (range 1.5 to 20 years).</td></tr>
<tr><td>Definitions</td><td>VOC: a hospitalisation requiring parenteral narcotics that was not attributable to other causes.
ACS: the presence of a new pulmonary infiltrate in combination with fever, chest pain or respiratory symptoms.
Elevated $sPLA_2$: 100 ng/mL on the basis of findings from other studies</td></tr>
<tr><td>Prognostic factors and confounders</td><td>Clinical variables: none reported
Laboratory variables: $sPLA_2$
Outcome of interest: development of ACS
Confounders: No potential confounders reported and none adjusted for in analysis</td></tr>
<tr><td>Length of follow up</td><td>During hospitalisation</td></tr>
<tr><td>Location</td><td>USA/Netherlands (unclear details of institution)</td></tr>
<tr><td>Outcomes measures</td><td>$sPLA_2$</td></tr>
<tr><td>Results</td><td>Predictive value of $sPLA_2$ in acute chest syndrome:
<table>
<tr><th></th><th>Sensitivity</th><th>Specificity</th><th>PPV</th><th>NPV</th><th>Accuracy</th></tr>
</table>
</td></tr>
</table>

$sPLA_2$ alone	100	67	55	100	76
$sPLA_2$ + fever	100	87	75	100	90
$sPLA_2$ + chest pain	50	80	50	80	71
$sPLA_2$ + respiratory symptoms	67	100	100	88	90
$sPLA_2$ + auscultatory findings	67	100	100	88	90

Of the 21 patients who had VOC admissions in the study, 6 went to develop ACS. With the use of a threshold value of 100 ng/mL, $sPLA_2$ concentration was elevated in all patients who developed ACS in the 24 to 48 hours before this diagnosis was made clinically. The maximal $sPLA_2$ concentration for the ACS group (mean 849 ng/mL; median 399 ng/mL) was significantly higher than for uncomplicated VOC (mean 132 ng/mL; median 88 ng/mL, p = 0.009). Comparing the frequency of an elevated $sPLA_2$ in the two groups in the first 3 days revealed that ACS patients were more than 20 times more likely to have an elevated $sPLA_2$ than VOC patients (OR = 24.8, CI 1.168-527.5, p = 0.023)

Authors' conclusion	The data indicate that $sPLA_2$ can be useful in alerting the clinician to patients with impending ACS. In addition, $sPLA_2$ may be useful for instituting early therapies to prevent or reduce the clinical morbidity of ACS.
Source of funding	Supported in part by grants from the National Institutes of Health
Comments	All patient care was overseen by paediatric house staff and a paediatric haematologist/ oncologist, who were unaware of the study. Patients with VOC are treated under a standardised clinical practice guideline that includes incentive spirometry. Personnel performing the $sPLA_2$ were blinded to the clinical status of patients. Sensitivity, specificity, PPV and NPV were calculated only on levels obtained in the three days before ACS was clinically diagnosed. Unvalidated threshold reported.

Table 62 Evidence table for Lewing et al (2011)

Bibliographic reference (Ref ID)	Lewing et al 2011 (Ref ID: 3478)
Type of prognostic study & aim	Study type: Retrospective chart review Aim: To investigate whether nalbuphine may promote less sedation, less hypoventilation and potentially less episodes of ACS after painful episodes
Number and characteristics of patients	Total: 796 admissions for painful episode were assessed from 2 centres Inclusion: Patients admitted with the diagnosis of SCD and acute painful episode with a baseline chest x-ray on admission from two institutions Exclusion: patients hospitalised for just fever were excluded Patient characteristics: Both centres were comparable with regards to their average number of patient admissions per year for painful episode, with similar distribution of the sickle haemoglobinopathies and similar male to female ratios. Age ranged from 3 to 19 years in the institution which used morphine (St Louis) and ranged from 4 to 20 years in the institution which used nalbuphine.

Definitions	ACS: based on definition used by the National Acute Chest Syndrome Study Group-patients required to have chest pain; some evidence of respiratory compromise or distress (tachypnea, hypoxia or increased work of breathing); and new infiltrate lesion on chest x-ray. Fever was not a required criterion, but evidence of such was recorded. Narcotic choice used to treat painful episode: the centre in St Louis primarily used morphine with a starting dose of 0.01 mg/kg/h whereas the centre in Kansas City primarily used parenteral nalbuphine with a usual starting dose of 0.075 mg/kg/h continuous infusion.
Prognostic factors and confounders	Clinical variables: narcotic use (morphine vs. nalbuphine) Laboratory variables: none reported Outcome of interest: development of ACS Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	During hospitalisation (chart review 2000 and 2001)
Location	USA (in two children's hospitals in Missouri)
Outcomes measures	Narcotic use
Results	Incidence (regardless of narcotic use): Combining the 2 years yields an incidence of ACS in St Louis of 9.7% and 4.8% in Kansas. The difference in incidence of 4.9% (95% CI 1.7% to 8.1%, p = 0.003) Incidence (with reference to narcotic use): The incidence of ACS in the morphine group was more than 4 times higher when compared with the nalbuphine group (10.8% vs. 2.1%, p < 0.0001, CI 5.4 to 12.5)
Authors' conclusion	When nalbuphine is used alone as the single parenteral opioid agent to treat painful episodes in patients with sickle cell disease, the incidence of ACS is less than when compared with other opioids used to treat pain. An randomised, double blind prospective study needs to be implemented to obtain the true difference between these two narcotics.
Source of funding	Not reported
Comments	The two institutions chosen for this study were similar with regards to geography, climate and patient demographics such that both facilities were university based programs within a city of similar size in the same state, having approximately the same number of hospitalisations for sickle cell painful episodes per calendar year. The modes of administration of the individual narcotic differed (i.e. continuous infusion vs. bolus dosing) and 2 different treatment centres were involved. Patients with repeat episodes of ACS were not evaluated separately and differences in analgesic regimen for patients with multiple admissions cannot be determined from the data.

Table 63 Evidence table for Audard et al (2010)

Bibliographic reference (Ref ID)	Audard et al 2010 (Ref ID: 111)

Type of prognostic study & aim	Study type: Retrospective cohort study Aim: To retrospectively estimate the incidence and to study the risk factors for acute kidney injury (AKI) at hospital admission and to prospectively analyse the possible association between haemodynamic alterations (assessed using thransthoracic echocardiography) and the occurrence of AKI at ICU admission
Number and characteristics of patients	Total: 254 episodes of vaso-occlusive complication in 161 SCD patients who were admitted to hospital (174 episodes of painful crisis in 103 patients, 58 episodes of moderate ACS in 42 patients and 22 episodes of severe ACS in 16 patients) Inclusion: SCD patients hospitalised in author's institution for vaso-occlusive complications. No other specific details reported Exclusion: Patients without available biological data allowing AKI classification and those with pre-existing chronic kidney damage were excluded from the analysis. Patient characteristics: At hospital admission, the WBC ($p < 0.01$), aspartate aminotransferase ($p = 0.04$), alanine aminotransferase ($p < 0.01$), total bilirubin ($p = 0.02$), direct bilirubin ($p = 0.04$) and lactate dehydrogenase levels (p , 0.01) were significantly higher for ACS episodes compared with uncomplicated pain crisis. Age ranged from 22 to 32 and the majority of patients (86.7% in those without AKI and 100% in those with AKI) had the SS genotype.
Definitions	AKI: measured according to AKIN criteria (3 stages of AKI). Stage 1 is an increase in serum creatinine of ≥ 26.4 µmol/L or increase to ≥ 150-200% from baseline, stage 2 is an increase in serum creatinine to > 200-300% from baseline and stage 3 is an increase in serum creatinine to >300% from baseline or serum creatinine ≥ 354 µmol/L with an acute increase of at least 44 µmol/L. Serum creatinine levels were measured at hospital admission or ICU admission and were compared with baseline values (the lowest serum creatinine measured during the 3 months preceding hospitalisation Uncomplicated pain crisis (PC): an episode of pain that affected long bones, ribs, pelvis, sternum, or the abdomen without pulmonary symptoms. Moderate ACS: presence of fever or chest pain accompanied by the appearance of new pulmonary infiltrates on the chest x-ray Severe ACS: when ACS was accompanied by signs of severity requiring ICU admission as previously reported (Dessap et al 2008). Baseline characteristics: measured during the 3 months preceding hospitalisation
Prognostic factors and confounders	Clinical variables: baseline characteristics (sex, age, BMI, genotype, past medical history and treatments) Laboratory variables: white cell count, total haemoglobin, platelet count, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, lactate dehydrogenase and echocardiography data Outcome of interest: Development of AKI Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	During hospitalisation (retrospective study period: January 2004 to December 2004 and prospective study period: January 2004 to September 2006.)
Location	France (in a University Teaching Hospital which houses a SCD centre)
Outcomes measures	sex, age, BMI, genotype, past medical history and treatments, white cell count, total haemoglobin, platelet count, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, lactate dehydrogenase and echocardiography data
Results	Incidence of AKI: Overall AKI occurred in 11 (4.3%) episodes (corresponding to 11 different patients) and included 10 cases in stage 1 and one case in stage 2. The incidence of AKI was 2.3% during uncomplicated PC, 6.9% during moderate ACS and 13.6% during severe ACS ($p = 0.03$). Two patients with AKI had

received NSAIDs before hospital admission.

Laboratory values at admission (n = 254 episodes) in relation to whether patients experienced AKI:

Laboratory values (white cell count, total haemoglobin, platelet count, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, lactate dehydrogenase) at hospital admission were similar between patients who developed AKI and those who did not (AKI = 11, no AKI = 243, all p > 0.05).

Baseline characteristics of patients in relation to whether they experienced at least one episodes of AKI (n = 161 patients):

	AKI during at least one vaso-occlusive complication (medians with 25th and 75th percentiles)		
Parameter	**No (n = 150)**	**Yes (n = 11)**	**P-value**
White blood cell count 10^9/L	9.8 (7.8-11.6)	11.9 (9.0-15.2)	0.03
Total haemoglobin g/dL	8.9 (8.2-9.9)	8.2 (7.9-8.6)	0.04
Lactate dehydrogenase IU/L	325 (257-427)	453 (322-664)	0.02

Patients who developed AKI during at least one vaso-occlusive episodes had lower baseline haemoglobin levels and higher baseline white cell counts and lactate dehydrogenase compared to patients who did not develop AKI. There were no significant differences with other baseline characteristics (sex, age, BMI, genotype, past medical history and treatments, all p > 0.05). The renal function recovered at the follow-up assessment in 9/11 patients who developed AKI during hospitalisation. One patient remained with increased creatinine vales and another patient developed chronic renal failure requiring long-term dialysis.

Association between haemodynamic profile and AKI occurrence in patient with severe ACS (n = 65 episodes):

	AKI during severe ACS (medians with 25th and 75th percentiles)		
Parameter	**No (n = 59)**	**Yes (n = 6)**	**P-value**
Aspartate aminotransferase IU/L	36 (25-59)	275 (70-904)	<0.01
Alanine aminotransferase IU/L	27 (15-36)	223 (37-490)	<0.01
Total bilirubin µmol/L	68 (45-99)	173 (78-300)	0.04
Direct bilirubin µmol/L	18 (10-44)	100 (56-167)	0.03
Lactate dehydrogenase IU/L	443 (349-670)	980 (488-2400)	0.04

Patients with AKI had higher aminotransferase, bilirubin and lactate dehydrogenase levels at ICU admission than patients without AKI. There were no significant differences with other laboratory parameters (white cell count, total haemoglobin, platelet count, alkaline phosphatase and arterial blood gases, all p > 0.05)

<table>
<tr><td></td><td>Echocardiography data of patients with severe ACS at ICU admission in relation to whether they experienced AKI (n = 65 episodes):
<table>
<tr><td></td><td colspan="2">AKI during severe ACS (medians with 25th and 75th percentiles)</td><td></td></tr>
<tr><td>Parameter</td><td>No (n = 59)</td><td>Yes (n = 6)</td><td>P-value</td></tr>
<tr><td>IVC collapse %</td><td>16 (3-38)</td><td>0 (0-6)</td><td>0.02</td></tr>
<tr><td>Tricuspid regurgitant jet velocity m/s</td><td>2.8 (1.8-3.2)</td><td>3.6 (3.1-3.9)</td><td>0.01</td></tr>
<tr><td>Systolic pulmonary artery pressure mmHg</td><td>46 (28-54)</td><td>67 (54-74)</td><td>0.01</td></tr>
<tr><td>Cor pulmonale[a] n (%)</td><td>5 (8.5%)</td><td>4 (66.7%)</td><td><0.01</td></tr>
</table>
IVC, inferior vena cava
a defined by association of a dilated right ventricle and paradoxical motion of the interventricular septum

Patients with AKI had lesser inferior vena cava collapse, higher tricuspid regurgitant jet velocity and higher systolic pulmonary artery pressure than patients without, whereas the E/A ratio, left ventricle ejection fraction, stroke index and cardiac index were similar between groups (all p > 0.05).</td></tr>
<tr><td>Authors' conclusion</td><td>AKI incidence during VOC complications of SCD is relatively low (< 5%) and appears to be confined to be confined to patients with ACS and pulmonary hypertension. These findings suggest a pathophysiological process involving right ventricular dysfunction and venous congestion.</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>Retrospective analysis of clinical and biological data from SCD patients</td></tr>
</table>

Table 64 Evidence table for Baumgartner et al (1989)

Bibliographic reference (Ref ID)	Baumgartner et al 1989 (Ref ID: 2536)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a retrospective chart review Aim: To establish parameters to distinguish between sickle cell crisis and intra-abdominal infection
Number and characteristics of patients	Total: 53 patients with sickle cell anaemia presenting to the emergency room with abdominal pain (from 136 patients who presented to the emergency room with pain). 30 of these 53 patients had pain due to sickle crisis, 12 had pain due to chloecystitis or acute appendicitis, 7 had pain due to papillary necrosis/ pyelonephritis and 3 had pain due to gynaecologic disorders. Inclusion: patients with sickle cell anaemia presenting to the emergency room with abdominal pain. No other details reported. Exclusion: No details reported Patient characteristics: Their mean age was 23.4 ± 9.5 years and 30% were men. Their genotypes were SS (62%), SC (15%), SA (11.5%) and S-other (11.5%). No statistical testing of differences between groups.

<table>
<tr><td>Definitions</td><td>No specific definitions reported.</td></tr>
<tr><td>Prognostic factors and confounders</td><td><u>Clinical variables:</u> pain distribution (coexistent abdominal and remote pain, location of pain), historical factors (duration, emesis, similarity to prior crises, precipitating event, prior abdominal operation), physical findings (temperature, icterus, peritoneal signs, pain relief with hydration and oxygen ≤ 48 hours)
<u>Laboratory variables:</u> haematocrit, WBC, lactate dehydrogenase (LDH), bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), pro time
<u>Outcome of interest:</u> acute surgical abdomen (also report analyses for gynaecologic and urologic process which are not reported in the evidence table)
<u>Confounders</u>: No potential confounders reported and none adjusted for in analysis</td></tr>
<tr><td>Length of follow up</td><td>During hospitalisation</td></tr>
<tr><td>Location</td><td>USA (admitted to Harbor-UCLA medical centre)</td></tr>
<tr><td>Outcomes measures</td><td>pain distribution (coexistent abdominal and remote pain, location of pain), historical factors (duration, emesis, similarity to prior crises, precipitating event, prior abdominal operation), physical findings (temperature, icterus, peritoneal signs, pain relief with hydration and oxygen ≤ 48 hours), haematocrit, WBC, lactate dehydrogenase (LDH), bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), pro time</td></tr>
<tr><td>Results</td><td>Note: analysis for gynaecologic, urologic and pneumonia are not reported in this evidence table
<u>Etiology of the abdominal pain:</u>
The abdominal pain was secondary to a sickle cell crisis in 30/53 (57%) patients and to a surgical abdomen (i.e. cholecystitis or appendicitis) in 12/53 (23%) patients. Of the 12 patients whose abdominal pain was due to a surgical entity, nine had pain due to chronic and/or acute cholecystitis (75%) and four had pain due to acute appendicitis.
<u>Pain distribution:</u>
<table>
<tr><th></th><th>VOC (n = 30)</th><th>Acute surgical process (n = 12)</th></tr>
<tr><td>Coexistent abdominal and remote</td><td>77%</td><td>0% (p < 0.005)</td></tr>
<tr><td>Location</td><td></td><td></td></tr>
<tr><td>Diffuse abdominal</td><td>50%</td><td>0%</td></tr>
<tr><td>Joint/extremity</td><td>43%</td><td>0%</td></tr>
<tr><td>Chest/back</td><td>50%</td><td>0%</td></tr>
<tr><td>Right lower quadrant (RLQ)</td><td>3%</td><td>17%</td></tr>
<tr><td>Right upper quadrant (RUQ)</td><td>7%</td><td>75%</td></tr>
</table>
<u>Historical factors:</u>
<table>
<tr><th></th><th>VOC (n = 30)</th><th>Acute surgical process (n = 12)</th></tr>
<tr><td>Duration (before presentation) ± SD</td><td>2.1 days ± 2.7</td><td>Cholecystitis: 15 wk ± 19 wk
Appendicitis: 2.3 ± 1.5 days</td></tr>
</table></td></tr>
</table>

	Emesis	23%	25%
	Similarity to prior crises	70%	8% ($p < 0.005$)
	Precipitating event	50%	0% ($p < 0.01$)
	Prior abdominal operation	33%	0%

Physical findings:

	VOC (n = 30)	**Acute surgical process (n = 12)**
Temperature (°F)	99.1 ± 1.00	99.5 ± 1.38*
Icterus	20%	25%
Peritoneal signs	13%	17%
Pain relief with hydration and oxygen (≤ 48 hours)	97%	0% ($p < 0.005$)

* For acute appendicitis 101.2 ± 2.2 ($p < 0.01$)

Laboratory findings:

	VOC (n = 30)	**Acute surgical process (n = 12)**
Haematocrit (%)	26.2 ± 6.8	32.1 ± 7.1
WBC (x 10^9/L)	16.4 ± 7.2	13.4 ± 4.8
lactate dehydrogenase (LDH) IU/L	381 ± 183	352 ± 126
Bilirubin (mg%)	1.96 ± 1.2	2.84 ± 1.75
Alkaline phosphatase	83.4 ± 42.9	75.3 ± 30.4
serum glutamic oxaloacetic transaminase (SGOT),	44.1 ± 27.0	34.9 ± 27.3
Pro time (sec)	12.1 ± 1.2	11.6 ± 1.0

Authors' conclusion	Based on the results of this review of patients with sickle cell anaemia having abdominal pain, the history and physical examination were the primary factors distinguishing surgical processes from vaso-occlusive phenomena. Specifically, localised abdominal pain, similarity to prior crises, lack of a precipitating event and lack of pain relief with hydration and oxygen were hallmarks of surgically correctable lesions in these patients. Laboratory tests were of lesser utility in distinguishing between the two processes.
Source of funding	Not reported
Comments	No details provided on data collection methods. Chronic and/or acute cholecystitis is included.

Table 65 Evidence table for (Berger et al 2009)

<table>
<tr><td>Bibliographic reference (Ref ID)</td><td>Berger et al 2009 (Ref ID: 330)</td></tr>
<tr><td>Type of prognostic study & aim</td><td>Study type: Prognostic factor/ explanatory study using a case-control study design
Aim: To identify clinical and laboratory features predictive of osteomyelitis in children with sickle cell disease and bony pain</td></tr>
<tr><td>Number and characteristics of patients</td><td>Total: 31 cases (from 70 case patients with SCD and discharge diagnosis of osteomyelitis) met the inclusion criteria and 93 controls
Inclusion: Patients aged 18 years and younger who were admitted to the hospital (see definition of cases and controls)
Exclusion: cases were excluded from the study if the patient was treated with antibiotics for less than 2 consecutive weeks, because this would indicate that the responsible physician did not treat the patient as a true case of osteomyelitis. Cases were also excluded if the patient had chronic osteomyelitis, rather than an acute presentation.
Patient characteristics: There were no significant differences between cases and controls in terms of age (8.9 vs. 8.5 years), sex (17 vs. 57 female) and genotype of SCD (all p > 0.05).</td></tr>
<tr><td>Definitions</td><td>Cases: patients with SCD who had 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.
Controls: patients with SCD who were admitted with a discharge diagnosis of VOC in the same year as the case. For each case included in the study, 3 randomly selected control participants were matched by year of admission.</td></tr>
<tr><td>Prognostic factors and confounders</td><td>Clinical variables: duration of fever before presentation, duration of pain before presentation, number of painful sites, presence of swelling
Laboratory variables: WBC count
Outcome of interest: development of osteomyelitis
Confounders: multivariate analysis carried out (no other adjustments reported), controls matched to cases by year of admission</td></tr>
<tr><td>Length of follow up</td><td>(study period January 1988 to December 2005)</td></tr>
<tr><td>Location</td><td>Canada (admitted to the Hospital for Sick Children)</td></tr>
<tr><td>Outcomes measures</td><td>duration of fever before presentation, duration of pain before presentation, number of painful sites, presence of swelling, WBC count</td></tr>
<tr><td>Results</td><td>Multivariate logistic regression:
<table>
<tr><th>Variable</th><th>OR (95% CI)</th><th>P-value</th></tr>
<tr><td>No. of days of fever before admission</td><td>1.8 (1.2-2.6)</td><td>0.004</td></tr>
<tr><td>No. of days of pain before admission</td><td>1.2 (1-1.4)</td><td>0.02</td></tr>
<tr><td>Swelling of affected limb on presentation</td><td>8.4 (3.5-20.0)</td><td>< 0.001</td></tr>
<tr><td>No. of painful sites (each additional painful site if more than one site was present)</td><td>0.7 (0.5-1.0)</td><td>0.03</td></tr>
</table></td></tr>
</table>

	A WBC count was not found to be a significant prognostic factor for osteomyelitis in the multivariate analysis.
Authors' conclusion	This case-control study of paediatric patients with SCD had identified risk factors that are predictive of an increased risk of osteomyelitis. Multivariate logistic regression analysis showed that the number of days of fever and pain before admission, swelling of the affected limb and number of painful sites remained significant predictors of osteomyelitis.
Source of funding	None reported
Comments	No criterion standard for the diagnosis of osteomyelitis.

Table 66 Evidence table for Buchanan et al (1978)

Bibliographic reference (Ref ID)	Buchanan et al 1978 (Ref ID: 3202)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a prospective cohort (some laboratory details obtained from chart reviews) Aim: To investigate the use of total and differential WBC in helping to identify bacterial infection in the febrile child with SCD
Number and characteristics of patients	Total: Laboratory values determined in 88 asymptomatic outpatients assessed in steady state who had no recent history of VOC or infection. Leukocyte counts were determined in 27 patients (35 episodes) of vaso-occlusive crisis and 13 patients (16 episodes) of bacterial infection Inclusion: No details reported Exclusion: No details reported Patient characteristics: Age ranged from 5 months to 21 years. None of the children were receiving transfusions or medications other than folic acid. 58 patients had SS genotype, 22 patients had SC genotype and 8 patients had Sβ-thal genotype. Leukocyte counts were determined in 40 children during VOC (35 episodes) and documented bacterial infection (16 episodes). In most instances, patients with painful crisis were hospitalised for symptoms of diffuse abdominal and/or musculoskeletal, and in no case was there evidence of associated infection
Definitions	Steady state: period when the patient is free of infection, crisis or other acute problems
Prognostic factors and confounders	Clinical variables: none reported Laboratory variables: WBC (total, segmented polymorphonuclear neutrophils PMN, and band or nonsegmented neutrophils) Outcome of interest: development of bacterial infection Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	During hospitalisation
Location	USA (no details of institution reported)
Outcomes	WBC (total, segmented polymorphonuclear neutrophils PMN, and band or nonsegmented neutrophils)

<table>
<tr><td>measures</td><td></td></tr>
<tr><td>Results</td><td>Types of bacterial infections:
Infections included haemophilus influenza, streptococcus pneumonia, staphylococcus aureus, Escherichia coli, Group A β-haemolytic streptococci, salmonella (14 cases had positive blood cultures)
Total and differential WBC (mean ± SD and range):
<table>
<tr><th></th><th>No of patients</th><th>Total WBC</th><th>Segmented PMN</th><th>Nonsegmented PMN</th></tr>
<tr><td>Vaso-occlusive crisis</td><td>27 (35 episodes)</td><td>16.4 ± 5.5 (9.4-36.0)</td><td>10.3 ± 2.4 (4.6-24.8)</td><td>0.32 ± 0.45 (0-3.23)</td></tr>
<tr><td>Bacterial infection</td><td>13 (16 episodes)</td><td>22.0 ± 10.7 (5.5-44.8)</td><td>10.4 ± 4.7 (1.15-21.8)</td><td>4.58 ± 2.8 (0.27-12.0)</td></tr>
</table>
There was no association between the band count and type 2 infecting organism or the site of infection.</td></tr>
<tr><td>Authors' conclusion</td><td>On the basis of this data, we believe that total and differential leukocyte counts are of value for identifying those children with potentially serious bacterial infections</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>No specific patient characteristics reported for children in VOC and no testing between groups. Unclear if patients with bacterial infection were presented with VOC.</td></tr>
</table>

Table 67 Evidence table for Ander et al (1997)

Bibliographic reference (Ref ID)	Ander et al 1997 (Ref ID: 1894)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a retrospective clinical study Aim: To determine if clinical signs and symptoms could be used to determine the necessity of an empiric workup of patients presenting with vaso-occlusive pain crisis
Number and characteristics of patients	Total: 38 patients with a total of 94 patient visits (39 patients with 100 patient visits were eligible) with 6 diagnosis of pneumonia (9/94 suggestive chest x-rays, the remaining three were diagnosed with sickle cell crisis alone) Inclusion: patients at least 18 years of age with a previous diagnosis of SCD and presenting to the ED with pain typical of VOC were eligible to take part. Exclusion: antipyretic use within 6 hours of ED presentation, pregnancy, and concurrent antibiotic use Patient characteristics: 21 were male with a mean age of 30 ± 7 years and 17 were female with a mean age of 33 ± 9 years. Of the 94 patient visits, 45 resulted in hospital admissions.
Definitions	Pneumonia: the presence of an infiltrate and a positive clinical response to a course of antibiotics. UTI: > 100000 colony forming units (CFU)/mL on urine culture. Vaso-occlusive pain crisis: diagnosis was confirmed via a physical examination and history of complaints, including severe chest, extremity, back or abdomen pain

Prognostic factors and confounders	Clinical variables: systemic symptoms (fever, chills, nausea/vomiting and URI), pulmonary symptoms (cough, short of breath, sputum, chest pain, haemoptysis) and urinary symptoms (dysuria, frequency, urgency, flank/back pain, suprapubic pain) Laboratory variables: none reported Outcome of interest: development of pneumonia Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	(study period of 18 months)
Location	USA (in an inner city, teaching ED)
Outcomes measures	systemic symptoms (fever, chills, nausea/vomiting and URI), pulmonary symptoms (cough, short of breath, sputum, chest pain, haemoptysis)
Results	*Note*: only results for pneumonia are reported in this evidence table Signs and symptoms: Review of the documented signs and symptoms for pneumonia found that all patients with pneumonia (n = 6) had at least 4/9 signs and symptoms included on the questionnaire. The sensitivity, specificity, PPV and NPV for having 4 out of the 9 diagnostic signs and symptoms were 100%, 87.5%, 35.3% and 100%
Authors' conclusion	It appears from this preliminary data that sickle cell vaso-occlusive crisis patients with no clinical evidence of pneumonia by history and physical examination may not require further diagnostic evaluation.
Source of funding	Supported by a Henry Ford Hospital Graduate Medical Education Grant
Comments	The VOC was treated with analgesics and hydration at the discretion of the treating physician. Patients were admitted if a significant infectious etiology was suspected or the patient was not responsive to the ED management of the pain crisis. Treating physicians completed questionnaires addressing systemic, pulmonary and urinary tract symptoms of patients eligible.

Table 68 Evidence table for Pollack et al (1991)

Bibliographic reference (Ref ID)	Pollack et al 1991 (Ref ID: 2393)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a prospective clinical study Aim: to determine the usefulness of obtaining routine chest radiographs and urinalyses on adults presenting to the emergency department in acute sickle cell pain crisis.
Number and characteristics of patients	Total: 71 patients with 134 separate visits for sickle cell pain were enrolled and 8 cases of pneumonia were diagnosed Inclusion: All patients presenting to the emergency department at the institution with a history of SCD and acute non-traumatic pain were entered into the protocol. Exclusion: conditions of exclusion from subsequent analysis were no record of previous haemoglobin electrophoresis for genotype characterisation of the patient's SCD and no previous chest radiographs for comparison with study films

	Patient characteristics: 55 patients (109 presentations) had documented HbSS, 10 (15 presentations) had HbSC and 6 (10 presentations) had HbSβ-thalassemia haemaglobinopathy.
Definitions	Bacterial pneumonia: diagnosis made in patients with fever, pulmonary infiltrate on chest radiography not present on previous films and subsequent response to antibiotics. UTI: diagnosis made in patients with > 100000 bacterial colonies on urine culture, regardless of whether they were symptomatic.
Prognostic factors and confounders	Clinical variables: systemic symptoms (fever, chills, nausea, vomiting, diarrhoea, upper respiratory infection), pulmonary symptoms (chest pain, cough, haemoptysis, shortness of breath), urinary tract symptoms (dysuria, urinary frequency, haematuria, flank/back pain, vaginal discharge, hesitancy), location of pain (chest, back/flank, extremities, abdomen, neck, head), temperature on presentation Laboratory variables: average WBC, haematocrit, peripheral reticulocyte count, peripheral absolute neutrophil count, urine PH, urine specific gravity Outcome of interest: development of pneumonia Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	During hospitalisation
Location	USA (university hospital ED)
Outcomes measures	systemic symptoms (fever, chills, nausea, vomiting, diarrhoea, upper respiratory infection), pulmonary symptoms (chest pain, cough, haemoptysis, shortness of breath), urinary tract symptoms (dysuria, urinary frequency, haematuria, flank/back pain, vaginal discharge, hesitancy), location of pain (chest, back/flank, extremities, abdomen, neck, head), temperature on presentation, average WBC, haematocrit, peripheral reticulocyte count, peripheral absolute neutrophil count, urine PH, urine specific gravity
Results	Clinical symptoms and temperature: 3 patients diagnosed with pneumonia complained of shortness of breath (37.5% vs. 20.9% overall, $p < 0.05$). All other clinical symptoms did not significantly differ between patients diagnosed with pneumonia and those who had not been diagnosed with pneumonia (all $p > 0.05$). Laboratory data: The average reticulocyte count for pneumonia patients was 18.6 ± 10.9% whereas the population average was 13.7 ± 8.4% ($p < 0.05$). All other laboratory factors did not significantly differ between patients diagnosed with pneumonia and those who had not been diagnosed with pneumonia (all $p > 0.05$).
Authors' conclusion	In sickle cell disease patients with pain crisis, routine chest radiography and urinalysis may be clinically useful and cost effective in the early diagnosis of crisis related infection
Source of funding	Not reported
Comments	Protocol involved questionnaire providing a detailed history of the sickle cell pain crisis (location of pain, presence of fever and other constitutional symptoms etc.) Patients had a CBC, routine urinalysis chest radiographs, oral temperature on arrival and review of documented physical examination. Chest radiographs were interpreted by staff radiologists. Charts were reviewed retrospectively for documentation of abnormal auscultatory findings on chest examination, microscopic evaluation of sputum (when performed) and abdominal and flank tenderness.

Table 69 Evidence table for Bernard et al (2008)

Bibliographic reference (Ref ID)	Bernard et al 2008 (Ref ID: 406)
Type of prognostic study & aim	Study type: Outcome prediction study using a retrospective observational study Aim: ED variables predictive of acute medical intervention would be derived from history, physical examination and vital signs, with routine laboratory and radiographic data adding little to the predictive model.
Number and characteristics of patients	Total: sample was randomly partitioned into derivation set (n = 94 patients with 670 visits) and validation set (n = 31 patients with 214 visits) set at the patient level (i.e. patient could only appear in the derivation or validation set but not both.) 199/284 admitted visits were found to have one or more of the outcomes. Inclusion: all sickle cell patient ED presentations to an urban academic centre and an urban community centre (patients identified by ICD-9 codes corresponding to sickle cell or vaso-occlusive crisis). Exclusion: patients were excluded if they were under 18 years of age. No other specific exclusion criteria are reported. Patient characteristics: There were 884 patient visits for 125 patients during the study period (median 3 visits per patient). The mean age was 36.3 years, 56 (45%) were male. The sickle variant was SS in 72 (57.6%), SC in 28 (22.4%), S-Thal in 12 (9.6%), sickle Los Angeles disease in one (0.8%), trait in one (0.8%) and unknown in 11 (8.8%). There were 197 admissions for transfusion or antibiotic administration, 71 for ACS and one for aplastic crisis. Of these events 33 (16.6%) were in patients returning to the ED after an initial visit that did not result in admission to hospital. The majority of ED visits were for sickle cell pain crisis.
Definitions	Acute chest syndrome: a new pulmonary infiltrate on chest radiograph in conjunction with at least one clinical sign of pulmonary disease (fever, tachypnoea, chest pain, shortness of breath, cough). At these institutions, patients meeting these criteria are sometimes diagnosed with pneumonia. Therefore, hospital discharge diagnosis was insufficient for the study outcome. Abnormal vital signs: temperature less than 36 or more than 38°C, pulse less than 60 or more than 100 beats per minute, respiratory rate less than 12 or more than 20 breaths per minute, systolic blood pressure less than 90 or more than 140 mm Hg, diastolic blood pressure less than 60 to more than 90 mm Hg and pulse oximetry less than 95% oxygen saturation.
Prognostic factors and confounders	Clinical variables: history (sickle cell variant), physical (chest pain, pain similar to previous, chills, temperature, pulse oximetry) Laboratory variables: Haemoglobin, nitrate, chronic vs. acute abnormality on chest x-ray Outcome of interest: hospitalisation with ACS, aplastic crisis, splenic sequestration and blood transfusion or antibiotic administration within 96 h of ED presentation Confounders: multivariate model constructed based on independently predictive variables (vital signs categorised as normal or abnormal, see definitions for more details)
Length of follow up	Within 96 hours of ED presentation (study period from 1st June 2004 to 31st May 2005)
Location	USA (presentations to an urban community centre and an urban academic centre)
Outcomes measures	history (sickle cell variant), physical (chest pain, pain similar to previous, chills, temperature, pulse oximetry), Haemoglobin, nitrate, chronic vs. acute abnormality on chest x-ray

Results

Note: Analysis was designed to determine if a risk score could be created based on vital signs, history and physical examination alone, and then to determine whether further diagnostic testing was useful or necessary.

Best fit multivariate model from history and physical examination:

Predictor	**Reference group**	**Odds ratio (95% CI)**
Sickle variant		
SC	S Thal	2.66 (1.12 to 6.31)
SS		2.31 (1.08 to 4.95)
Other/unknown		9.17 (3.56 to 23.65)
Chest pain	No chest pain	2.35 (1.55 to 3.57)
Pain similar to previous	Pain not similar to previous	0.60 (0.40 to 0.91)
Abnormal temperature	Temperature normal	4.37 (2.06 to 9.25)
Abnormal pulse oximetry	Pulse oximetry normal	4.72 (2.63 to 8.50)

The C-statistic for this model was 0.764 (95% CI 0.720 to 0.804)

Best fit multivariate model from history, physical examination and laboratory and imaging parameters:

Predictor	**Reference group**	**Odds ratio (95% CI)**
Sickle variant		
SC	S Thal	2.97 (1.15 to 7.65)
SS		1.95 (0.83 to 4.56)
Other/unknown		8.09 (2.84 to 23.08)
Chest pain	No chest pain	1.83 (1.13 to 2.97)
Pain similar to previous	Pain not similar to previous	0.54 (0.34 to 0.85)
Abnormal temperature	Temperature normal	5.35 (2.29 to 12.49)
Abnormal pulse oximetry	Pulse oximetry normal	3.56 (1.85 to 6.85)
Haemoglobin < 10	Haemoglobin ≥ 10	2.88 (1.68 to 4.94)
Nitrate positive	Nitrate negative	4.11 (1.35 to 12.56)
Chronic abnormality	Normal on chest x-ray	1.82 (1.01 to 3.27)
Acute abnormality		5.75 (2.69 to 12.31)

The C-statistic for this model was 0.854 (95% CI 0.823 to 0.886)

<table>
<tr><td></td><td>
Scoring system based on multivariate logistic regression model:
<table>
<tr><th colspan="2">Risk factor</th><th colspan="2">Score if present</th></tr>
<tr><td colspan="2">SS, SC other or unknown variant</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Chest pain</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Chills</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Pain not similar to pervious episodes</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Temperature < 36°C or > 38°C</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Oxygen saturation < 95%</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Haemoglobin <10</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Nitrates present in urinalysis</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Abnormalities observed on chest x-ray</td><td colspan="2">+ 1</td></tr>
<tr><td colspan="2">Total possible score</td><td colspan="2">9</td></tr>
<tr><td></td><td>Score > 2</td><td>Score > 4</td><td>Physician judgement</td></tr>
<tr><td>Overall accuracy</td><td>61.7 (54.8 to 68.2)</td><td>82.7 (76.8 to 87.4)</td><td>81.8 (75.8 to 86.6)</td></tr>
<tr><td>Sensitivity</td><td>86.0 (73.7 to 93.3)</td><td>49.1 (35.8 to 62.6)</td><td>77.2 (63.8 to 86.8)</td></tr>
<tr><td>Specificity</td><td>52.9 (44.8 to 60.8)</td><td>94.9 (89.9 to 97.6)</td><td>83.4 (76.5 to 88.7)</td></tr>
<tr><td>False negative rate</td><td>14.0 (6.7 to 26.3)</td><td>50.9 (37.4 to 64.2)</td><td>22.8 (13.2 to 36.2)</td></tr>
<tr><td>False positive rate</td><td>47.1 (39.2 to 55.2)</td><td>5.1 (2.4 to 10.1)</td><td>16.6 (11.3 to 23.5)</td></tr>
<tr><td>PPV</td><td>39.8 (31.2 to 49.1)</td><td>77.8 (60.4 to 89.3)</td><td>62.9 (50.4 to 73.9)</td></tr>
<tr><td>NPV</td><td>91.2 (82.9 to 95.9)</td><td>83.7 (77.3 to 88.6)</td><td>91.0 (84.8 to 94.9)</td></tr>
</table>
The area under the ROC curve for this score in the derivation set was 0.816 (0.778 to 0.854). In the validation set, the area under the curve was 0.824 (0.760 to 0.889)
</td></tr>
<tr><td>Authors' conclusion</td><td>This research demonstrates that variables predictive of adverse outcomes within 96 h of a sickle cell patient presenting to the ED can be identified. A simple risk score derived from these variables demonstrates reasonable accuracy in an independent sample. Prospective validation is necessary before any clinical decision making related to this score.</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>Data was abstracted by one of two emergency physicians using explicit definitions for each variable. Outcomes were captured by review of discharge diagnosis and hospital records for the current visit and by review of medical records for any repeat visits occurring within 96 h. The 96 h time frame was chosen to capture occult ACS related to the initial encounter and also represents a realistic time frame for outpatient follow-up. No specific protocols used for antibiotic administration and blood transfusion (subject to physician discretion). Not all patients were in sickle cell crisis. Not all patients received every diagnostic test.</td></tr>
</table>

Table 70 Evidence table for Chapman et al (2004)

Bibliographic reference (Ref ID)	Chapman et al 2004 (Ref ID: 1063)
Type of prognostic study & aim	Study type: Prognostic factor/ explanatory study using a retrospective chart review Aim: To determine whether blood counts discriminate between sickle cell pain episodes that lead to successful discharge from the emergency department and those that result in complications
Number and characteristics of patients	Total: Average 30 patients per year and 86 visits meeting the inclusion criteria. There were 48 patient visits with an uncomplicated course of illness and 38 patient visits with a complicated course of illness following a pain crisis. Inclusion: all patients from 0 to 18 years old who visited the ED in the 2 year period for vaso-occlusive crises related to their sickle cell anaemia. If a patient was seen in the ED more than once in a month, only the first visit was counted for inclusion in this study. Exclusion: patient presented with fever, chest pain or abdominal pain as these symptoms can be consistent with the more aggressive diagnoses of sepsis, ACS and splenic sequestration. Patients were also excluded if they had been transfused within 1 month of the ED visit of interest or if they were on chronic transfusion therapy. Patient characteristics: Patients' age ranged from 11 months to 18 years old, with a median age of 9.5 years. Groups were similar in terms of types of SCD, duration and severity of pain. The two groups were significantly different in terms of age ($p = 0.04$). In the complicated group, median age was 11.2 years and 55% were male. 66% had SS genotype while 26% and 8% had SC and other genotypes respectively. In the uncomplicated group, median age was 8.9 years and 65% were male. 61% had SS genotype while 29% and 10% had SC and other genotypes respectively.
Definitions	Admission: defined as hospital stay longer than 23 hours or admission to the hospital within 48 hours of the ED visit. Complicated pain crisis: defined as admission to the hospital, as the need for antibiotics or blood products either in the ED or within 48 hours of the Ed visit, or the development of ACS or aplasia within 48 hours of the ED visit. Uncomplicated pain crisis: defined as one leading to discharge from the ED without further medical contact within 48 hours Baseline measurements: considered the laboratory values of the 'well' visit to the clinic, such as for immunisations
Prognostic factors and confounders	Clinical variables: none specifically examined although demographic characteristics were presented (age, sex, genotype, duration and site of pain and median pain score) Laboratory variables: haemoglobin, reticulocytes, WBC, granulocytes, bands, ANC Outcome of interest: complicated or uncomplicated course Confounders: No potential confounders reported and none adjusted for in analysis
Length of follow up	During hospitalisation (study period January 1st 1999 to December 31st 2000)
Location	USA (tertiary care teaching institution with the only paediatric comprehensive sickle cell clinic in the region)
Outcomes measures	age, sex, sickle genotype, duration of pain, site of pain and median pain score, haemoglobin, reticulocytes, WBC, granulocytes, bands, ANC (including change from baseline for laboratory variables)

<table>
<tr><td>Results</td><td>
<u>Statistically significant patient characteristics associated with having complicated vs. uncomplicated course:</u>
<table>
<tr><th></th><th>Complicated course (n = 38)</th><th>Uncomplicated course (n = 48)</th><th>Odds ratio (95% CI)</th></tr>
<tr><td>Median age (range)</td><td>11.2 (4-18)</td><td>8.9 (0-18)</td><td>P = 0.04</td></tr>
<tr><td>Site of pain in arms</td><td>3</td><td>13</td><td>0.2 (0.04, 0.9)</td></tr>
</table>
There were no significant differences between complicated and uncomplicated courses for all other patient characteristics.
<u>Laboratory values:</u>
There was no significant difference between the laboratory values for patient visits with complicated versus uncomplicated pain crisis (all p ≥ 0.05).
<u>Statistically significant changes in laboratory values from baseline in uncomplicated vs. complicates sickle cell pain episodes:</u>
<table>
<tr><th></th><th>Complicated course (n = 38)</th><th>Uncomplicated course (n = 48)</th><th>Difference (95% CI)</th></tr>
<tr><td>Haemoglobin (g/dL)</td><td>-0.2</td><td>0.2</td><td>-0.4 (-0.8 to -0.1)</td></tr>
</table>
There were no significant differences between complicated and uncomplicated courses for all other changes in laboratory values (all p > 0.05). The changes in haemoglobin are close to the normal differences in laboratory values found on repeated measurements of blood values.
<u>Predictive model:</u>
Because older age and a fall in haemoglobin value from baseline appeared to be the strongest predictors of admission to hospital, a multivariate logistic regression model was constructed to determine if these variables could be combined to predict discharge or hospital admission. The resulting model fit the data poorly and was not helpful in predicting the outcomes of interest with an area under the curve of the ROC of only 0.68.
</td></tr>
<tr><td>Authors' conclusion</td><td>In conclusion, this study finds that screening complete blood counts, white blood cell differentials and reticulocyte counts in children presenting to the ED with vaso-occlusive crises do not help in predicting which patient visits will result in complications or require admission to hospital. A prospective study would help to solidify these conclusions.</td></tr>
<tr><td>Source of funding</td><td>None reported</td></tr>
<tr><td>Comments</td><td>ED management of sickle cell crises include hydration and parenteral pain medications. The treatment plan in the study ED has been formalised to the following: every patient with sickle cell disease and apparent vaso-occlusive crisis is evaluated within 15 to 30 minutes of arrival. An IV line placed for fluid hydration and for withdrawal of blood for laboratory evaluation. A loading dose of narcotics is given, as well as NSAID medications, either oral or parenteral. The patient is then re-evaluated every 20 minutes and receives ¼ to ½ bolus of the loading dose of narcotics until the pain has significantly diminished to a 0 or 1 out of a 5-point pain scale. Decisions to admit or discharge are made by the paediatric emergency medicine attending or fellow in conjunction with the patient and family. Generally, the patient is admitted to the hospital if the vaso-occlusive crisis has not been successfully treated within 3 to 4 hours of initiation of the above protocol. Charts were reviewed by 2 -/3 authors and all data entered by one reviewer. 10% of the charts were reviewed separately by two investigators for 9 parameters related to the study and inter-observer reliability was assessed by the kappa score. Group excluded (no laboratory data) were similar to those who were retained in the analysis.</td></tr>
</table>

Review question 4: Settings and skills for managing an acute painful episode

Table 71 Evidence table for Raphael et al (2008)

Bibliographic reference (Ref ID)	Raphael et al 2008 (Ref ID: 432)
Study type & aim	Retrospective cohort/ To determine whether day hospital (DH) management results in shorter length of stay (LOS) compared to inpatient care for patients experiencing uncomplicated vaso-occlusive crisis (VOC)
Number and characteristics of patients	N=70 patients (35 DH admissions and 35 inpatient admissions.) Nearly all patients in both groups were African-American and had Hb SS genotype. No statistical differences were observed in terms of pain scores, white blood cell count and haemoglobin at presentation. Severity of VOC as measured by pain score at initial presentation (mean pain score in day hospital patients = 7.9 and in inpatients = 8.2) Eight patients who initiated care in the DH required transfer to inpatient setting for severe, escalating pain or new symptoms. Mean age was 10.3 years in the day hospital and 13.6 years in inpatient setting. Exclusion: patients with secondary acute diagnoses including acute chest syndrome, new onset headache, or changes in neurological status at the time of initial presentation.
Definitions	Sickle Cell Disease (SCD): diagnosis of Haemoglobin (Hb) SS disease, Hb SC disease, Hb Sβ+ thalassaemia or Hb Sβ0 thalassemia. DH admission: Patients coming to the day unit for consecutive days are documented as admitted patients to DH. Any DH admission requiring transfer to inpatient care was still categorised as a DH admission and LOS was calculated by adding inpatient hospital days to those in the DH facility.
Intervention details	DH facilities: a five bed monitored unit which functions dually as an urgent care centre for pediatric haematology and oncology patients and a DH. Healthcare professionals: staffed by a supervising Haematology/Oncology board certified physician/nurse practitioner with nursing support. Admission: patients experiencing pain at home call the clinic and are triaged by a haematology nurse on duty. Medically stable patients experiencing uncomplicated pain crisis with or without fever are referred to the urgent care centre. Pain management: institutional sickle cell pain management protocol upon presentation and during admission. Procedure: following pain assessment and treatment, patients are monitored until 6pm. For patients stable enough to go home, the day's treatment course is converted into equivalents of an oral regimen of analgesics with the expectation that patients will return the next day for further aggressive care. Those who come for consecutive days in this manner are documented as admitted to the DH.

Comparison	Inpatient care: emergency department for treatment 24 hours a day. Healthcare professionals: managed by board certified pediatric emergency medicine physicians. Once admitted, patients are managed by general paediatricians. Pain management: institutional sickle cell pain management protocol upon presentation and during admission. Procedure: No details reported.
Length of follow up	The study period covered care from 2000 to 2006.
Location	USA
Outcomes measures	Return rate (readmission): The rate at which patients returned to the hospital for persistent symptoms of VOC for DH was 6% (2) at 48 hours compared to 0% for inpatient hospitalisations. LOS: Univariate analysis for LOS was reported and found location, sickle cell type, pain score, age and haemoglobin count were significantly associated with LOS (please see papers for details). Multivariate logistic regression (adjusted for sickle cell type, pain score and age) found the following factors were significantly associated with average LOS: location (outpatients RR 0.61, 95% CI 0.46 to 0.81, p = 0.0006), sickle cell type (SB+ [RR 0.29, 95% CI 0.12 to 0.69, p = 0.01], SB0 [RR 0.40, 95% CI 0.16 to 0.98, p = 0.05], SS [RR 0.53, 95% CI 0.33 to 0.84, p = 0.01]), pain score 9-10 (RR 1.54, 95% CI 1.08 to 2.19, p = 0.02) and age (RR 1.03, 95% CI 1.00 to 1.06, p = 0.03)
Authors' conclusion	DH care resulted in a 39% reduction of the average length of stay compared to inpatient admissions. We conclude that a dedicated DH facility has the potential to provide efficient and timely management of uncomplicated VOCs through reduction of LOS.
Source of funding	Not reported
Comments	To minimise selection bias, for each of the 35 patients with a DH admission, an inpatient admission patient was selected to match the admission date. Patient data were collected by chart review. Where care is initiated depends on patient choice for uncomplicated VOC. Therefore this study design was subject to selection bias as patients who perceive themselves as sicker may chose the emergency room as a point of entry for care as opposed to an outpatient facility. One day of care in DH may also not be equivalent of one day of care in an inpatient setting, therefore comparing LOS may not be appropriate. This study was only powered to determine the effect of location type. The first DH admission by each patient was extracted for this study (no multiple admissions) and an independent sample was selected for inpatient admission.

Table 72 Evidence table for Benjamin et al (2000)

Bibliographic reference (Ref ID)	Benjamin et al 2000 (Ref ID: 1623)
Study type & aim	Retrospective cohort/To decrease the load of the emergency department (ED) and to study the value of a dedicated facility with knowledgeable staff applying principle based individualised care.

Number and characteristics of patients	N=144 patients sought treatment for acute pain crisis during the first 5 years of the DH (2554 visits to DH and 2612 ED visits). 168/2033 of visits to DH and 776/1818 of visits to ED were admitted for uncomplicated pain. Median age was 30 years and 53% of these patients were male. No statistical analyses between DH and ED patient characteristics were reported. Exclusion: no specific exclusions were reported
Definitions	Frequent pain patients: patients who experienced more than 5 visits and more than 2 hospitalisations per year Uncomplicated pain population: patients admitted with only unrelieved pain and patients who were discharged home from ED or DH.
Intervention details	DH facilities: located in medical centre and includes a triage room, 3 beds and clinical laboratory for sample processing. Admission: patients presented either directly from home as walk-in visits or were transferred from the ED after an initial course of treatment. Healthcare professionals: No specific healthcare professionals are reported to be involved in care. It is reported that LOS comparisons were made between adult painful crisis patients without comorbidities (who were followed by DH physicians with house staff assistance) and LOS for patients followed by physicians not associated with the DH. Pain management and procedure: an assessment and treatment protocol was used. Patients were assessed by a nurse and physician prior to initiation of therapy. Assessment and treatment occurred within 15-20 minutes of patient's arrival at the DH. At half hour intervals, patients completed the rapidly administered assessment instruments through a sequential combination of nurse interview and self-administered questionnaire. Treatment decisions were made based on the responses. Specific procedures included; assessment of pain, selecting drug and loading doses, titrating medication to relief, using by the clock dosing to maintain relief, adjusting rescue dosing for breakthrough pain, combining drugs to enhance the efficacy/toxicity ratio, adjusting drugs for tolerance, evaluating, recording and treating adverse events, adjusting the method and route of drug delivery, identifying and treating precipitating factors and making dispositions based on response to therapy and the presence or absence of comorbidities.
Comparison	Inpatient care: patients were treated in ED when the DH was closed. There was no other reporting of when patients were treated in ED. Healthcare professionals: No details reported Pain management: No details reported Procedure: No details reported
Length of follow up	The time period covered in this paper is 1989-1993.
Location	USA

<table>
<tr><td>Outcomes measures</td><td>Descriptive analyses were reported for assessment and treatment, dose titration to relief and adverse effects and disposition and are summarised below (for more details please see paper). Statistical analyses were only conducted for patients treated within the DH.

Assessment and treatment: Patients reported moderate pain in 40% of DH visits and severe pain in 60% of visits. On a scale of 0-3, overall mean pain score was 2.7 and the median pain score was 3.0.

Dose titration to relief and adverse effects: Those patients with unrelieved pain (16%) were frequent pain patients. The overall mean relief score on a scale of 0-4 was 2.5 (frequent pain patients mean pain score 2.20, SD = 0.4, infrequent pain patients mean pain score 3.1, SD = 0.7, p < 0.0001.)

LOS: The average LOS in the DH was 4.5 hours (range 2 to 7 hours), while the average LOS in the ED was 13 hours (range 11 minutes to 90 hours). Treatment time in the ED before transfer to the DH decreased each year, ranging from 16 hours in year 1 to 8 hours in year 5.

Hospital admission rate:

Table 1-Admission rate for direct visits to the ED and DH
<table><tr><td></td><td colspan="4">Year</td></tr><tr><td>Facility</td><td>0 (baseline)</td><td>1</td><td>2</td><td>3-5</td></tr><tr><td>ED</td><td>92%</td><td>70%</td><td>49%</td><td>48%</td></tr><tr><td>DH</td><td>N/A</td><td>11%</td><td>2%</td><td>2%</td></tr></table>During the 5 years, an average of 51% of ED visits and 8% of DH visits were admitted to the hospital. The average ED admission rate decreased to 48% in years 2-5. When ED and DH visits were combined, 50% of the overall admissions represented a 40% decrease in admission rate since the opening of DH. Of patients with uncomplicated pain, 42.7% (776/1818) of ED patients were admitted to hospital and 8.3% (168/2033) of DH patients were admitted.

Impact of length of hospitalisation: Whether patients were admitted through DH or ED, LOS for patients with painful crises without comorbidities (and who were followed by DH physicians, with the assistance of the house staff) was reduced from 9.3 days in the first year to an average of 7.3 days in the fifth year (average 7.8 days per year over the 5 year period). The LOS for patients followed by private physicians who were not connected with the DH remained unchanged.</td></tr>
<tr><td>Authors' conclusion</td><td>A dedicated facility for the treatment of uncomplicated painful crisis, operating on principle based pain management, can reduce the time to pain relief, increase the number of patients discharged home, decrease the hospitalisation rates, lessen the use of ED help integrate care, and positively impact use in other areas. Hence a dedicated DH appears to be an advantageous multidisciplinary alternative care facility for the acute care of uncomplicated painful crises in SCD patients. The most critical elements include having a dedicated facility and leadership adapted to the various types, sizes, or locations of the institution.</td></tr>
<tr><td>Source of funding</td><td>Supported in part by grant from the National Institutes of Health, Bethesda, MD.</td></tr>
<tr><td>Comments</td><td>Comparisons between DH visits and dispositions of painful crises and those at the ED were made using DH database and hospital information systems. The ED admission rate in the year prior to the opening of the DH was taken as baseline. The ED also treats the majority of patients presenting with comorbidities as well as patients with uncomplicated pain. To adjust for this, the authors compared DH visits only with the portion of the ED population that is comparable to the uncomplicated painful crisis population which constitutes the majority of patients seen by the DH. 91% of ED visits were by patients who also had visits to DH</td></tr>
</table>

Table 73 Evidence table for Frei-Jones et al (2009)

Bibliographic reference (Ref ID)	Frei-Jones et al 2009 (Ref ID: 275)
Study type & aim	Prospective before and after study design/To prospectively reduce the 30 day readmission rate in children with SCD and pain
Number and characteristics of patients	N =124 children admitted for pain during a 6 month period (n = 68 in prospective cohort based on 89 inpatient admissions, n = 56 in control cohort based on 85 inpatient admissions) Patients in the prospective cohort were significantly more likely to have asthma as a comorbid condition (53%) than patients in the control cohort (46%, p = 0.001). There were no significant differences in terms of age, gender, SCD type other comorbities, baseline labs, number of hospitalisations and insurance status between the two groups. Mean age was 11.2 years in prospective cohort and 12.7 in the control group. Admission pain scores were not different between the intervention and control cohorts (8.6 vs. 8.3, p = 0.3, 95% CI -0.2 to 0.6). 12% of patients in intervention cohort and 22% of those in control cohort had Acute Chest Syndrome (ACS) as a primary discharge diagnosis. Inclusion: any diagnosis of SCD as confirmed by haemoglobin analysis, age > 12 months as pain requiring opioid administration is rarely the primary reason for admission in young children, and admission to the inpatient unit for further pain management. Exclusion: pain not requiring use of intravenous (IV) opioids, headache, group A Streptococcus infection, costochondritis, or priapism as the primary reason for admission and ≥12 hospitalisations for SCD related morbidity in the previous 12 months. The same inclusion and exclusion criteria were used to identify patients in the control cohort.
Definitions	Independent admission: a second admission for acute SCD pain that occurred within 30 days of a readmission visit but was greater than 30 days from the original admission for acute SCD pain. Readmission: hospital admission for any SCD related morbidity occurring ≤ 30 days after the primary admission for SCD pain. SCD pain: acute pain in the extremities, back, abdomen, or chest that is presumed to be due to SCD, with no other identified cause. Disease severity: patients with ≥3 hospitalisations for SCD related morbidity in a 1 year period Asthma symptoms: presence of chest pain, cough, hypoxia, wheezing, respiratory distress or decreased breath sounds in an asthmatic patient
Intervention details	Intervention cohort: received a multi-modal intervention which contained three components 1) standardised, evidence based SCD pain admission orders 2) a 30 minute small group in-service on SCD pain given monthly to all St. Louis Children's hospital house staff physician for 6 months (a physician with expertise in SCD led the session for all pediatric house staff physicians directly assigned to the inpatient floors where children with SCD were admitted) and, 3) patient/caregiver education by an inpatient nurse with expertise in SCD Procedure: There was a 5 month-run in period that occurred before the prospective cohort study was started to increase awareness among nurses, unit secretaries, and attending physicians to prevent lack of knowledge as a barrier to implementation. The house staff educational component was completed in the first 6 months of the academic year (July-December) where 98% of residents received the educational in-service. Pain assessment: Standard nursing assessment of pain was using a 10 cm visual analogue scale (VAS), the Wong Baker FACES scale or the modified Children's Hospital of Eastern Ontario Pain Scale (mCHEOPS) depending upon the age of the patient.

Comparison	Pre-intervention (control cohort): A similar seasonal time period (July 2006-December 2006) was chosen prior to the intervention for the control cohort to help exclude influenza and other infections as a cause of readmission. Pre-specified SCD pain orders were used in 32% of eligible admissions. No other details were reported about pre-intervention conditions or procedures.
Length of follow up	Intervention: 6 month intervention period (July 2007-December 2007) Control: 1 year prior to intervention (July 2006-December 2006) Follow-up after educational component is terminated: 6 months post-intervention (January 2008-June 2008)
Location	USA

Outcomes measures

30 day readmission rate during intervention (primary outcome): Readmission rates within 30 days were significantly lower for children admitted during the intervention period in comparison to the control period (11% vs. 28%, p < 0.002, 95% CI 0.1 to 0.6). Average LOS increased by less than 1 day after the intervention which was statistically significant but probably clinically irrelevant (5 vs. 4 days p = 0.03, 95% CI -1.8 to -0.1)

Importance of the educational component: 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 to 19% (33/173) vs. 28% (44/159), in the previous year (p = 0.06, 95% CI 0.4 to 1)

Other quality care measures (secondary outcomes): secondary outcomes assessed included PCA use, duration of IV pain medications, early weaning of analgesics within the first 24 hours not due to respiratory depression or side-effects, absolute admission and discharge pain scores. Selected outcomes are presented in the table below (for more details of other secondary outcomes please see full paper)

Table 1-Markers of quality care for intervention and control cohort

Marker of quality care	**Intervention cohort (n = 89)**	**Control cohort (n = 85)**	**P-value (95% CI if reported)**
Primary discharge diagnosis			
SCD painful episode	78 (88%)	66 (78%)	0.11
Acute Chest Syndrome (ACS)	11 (12%)	19 (22%)	0.11
Weaning of pain medications			
wean in first 24 hours	26 (29%)	26 (31%)	0.87
average time before weans (days)	2.4	1.8	0.39
Duration of oral meds prior to discharge			
less than 24 hours	52 (58%)	47 (55%)	0.76
Pain management			
Duration of IV meds (days)	4.5	3.6	0.35
Readmission			
readmission visits	10	24	0.007
time to readmission visit (days)	16	9.4	0.62
Readmission diagnosis			
SCD painful episode	6 (60%)	23 (96%)	0.02
Asthma	0	1	0.49
Fever	2	0	0.50
Pain scores			
average change in pain score on discharge	5.3	6.4	0.02 (-2.1 to -0.15)
discharge pain score	1.9	3.3	0.003 (0.3 to 1.5)
admission pain score	8.6	8.3	0.3 (-0.2 to 0.6)

The prevalence of opioid induced adverse effects on both groups were also reported but are not reported in the evidence table.

Authors' conclusion	A multi-modal intervention was successful in decreasing 30 day hospital readmission rate for children with SCD and pain. Provider education was the most important component of the multi-modal intervention (based on the observation that cessation of educational sessions resulted in return to the readmission rate prior to the intervention.)
Source of funding	NIH/NCRR Burroughs Wellcome Foundation
Comments	Pre-specified SCD pain orders were used in 93% of eligible admissions during the intervention period. 8 patients had multiple admissions for SCD pain during the study period and this may have biased the results to a higher readmission rate by giving one patient too much influence (all admissions were included).

Table 74 Evidence table for Adam-Graves et al (2008)

Bibliographic reference (Ref ID)	Adam-Graves et al 2008 (Ref ID: 4750)
Study type & aim	Before and after study/ To provide a model (providing one dedicated area) for inpatient SCD unit care
Number and characteristics of patients	Not reported
Definitions	N/A
Intervention details	Specialised SCD unit: ten inpatient rooms, a nursing station and conference and lounge areas. It is near the obstetrics floor to provide easy access to SCD patients who are pregnant. The unit is also equipped with SCD literature and computer based programs that allow patients and visitors access to information that will help them to understand the disease. Healthcare professionals: all nurses and support staff are required to take computer based education (CBE). Admission: direct admissions were allowed from home to the unit for acute and subacute SCD associated problems such as painful events, urgent blood therapy, fever and moderate to severe infections. Patients can be admitted via telephone triage. If admission is necessary, the patient is assigned a room number and can go directly to this room on arrival for further examination. Education: The SCD unit's medical director and physicians developed a nine-lesson, computer based education (CBE) for unit nurses. The nine lessons include an overview of SCD, three pain-specific modules, blood treatment, hypoxemia/ACS, line care, special procedures and therapeutic phlebotomy. The CBE program was launched with series of classroom lectures and workshops focusing on staff (all nurses and ancillary staff) that spend the most time with SCD patients in all areas of the hospital. Education was also given to house staff and medical residents. Procedure: The admitting doctor performs a history and physical examination and creates an individualised care plan. Disease specific protocols were developed by a multidisciplinary team for the SCD unit's admission process and patient care guidelines. Healthcare professionals advised to first take care of those who need blood and then to initiate pain treatment.

Comparison	Facilities: the MED is a 355 bed, non-profit institution staffed by the University of Tennessee College of Medicine. The hospital provides general medical and surgical services and specialised therapeutic care including neonatology, obstetrics and gynaecology, orthopaedics, oncology and trauma. Admission: Before the unit was set-up, SCD patients with acute or subacute SCD associated problems either presented to the emergency department or the outpatient sickle cell centre for initial consultation.
Length of follow up	In November 2004, the MED dedicated space for the adult SCD patient unit.
Location	USA
Outcomes measures	LOS: Average LOS decreased from 5.8 days in 2002 (pre-SCD unit) to 4.6 days in 2007 (post-SCD unit). Patient satisfaction outcomes were also reported but these were internal assessments after the unit had been set up.
Authors' conclusion	The model presented can be implemented in urban hospitals with an average daily census of five or more SCD inpatients. At Regional Medical Centre at Memphis (the MED) reorganisation of services led to improvement of access, care quality and treatment cost effectiveness for adults with SCD.
Source of funding	Not reported
Comments	None

Table 75 Evidence table for Jamison & Brown (2008)

Bibliographic reference (Ref ID)	Jamison & Brown 2008 (Ref ID: 1330)
Study type & aim	Before and after study/ To improve overall satisfaction of patients with SCD, reduce LOS and reduce the costs associated with hospital treatment of patients with SCD
Number and characteristics of patients	N = 204 (n = 94 patients admitted to the hospital with SCD crisis during the year (FY98) prior to the implementation and n = 110 patients admitted to the study hospital with SCD crisis during the year (FY00) that began 1 year after implementation of the new treatment program). No other details of patient characteristics are reported. Exclusion: patients who exceeded a 30-day stay or who were awaiting skilled care facility placement. Inclusion: no specific inclusion criteria was reported
Definitions	LOS: the average number of days the patient was hospitalised with a diagnosis of SCD with crisis. Patient visit (inpatient or outpatient): classified based on medicare criteria.

Intervention details	Admission/setting: when the new program was implemented, all patients with SCD were admitted to the oncology department because of (a) nurses' experience and knowledge of pain management (b) similar hematologic manifestations of SCD and cancer and (c) the oncology department's history of having high patient satisfaction scores. The study focused on 3 types of admission: 1) admission through the ED with initiation of the treatment protocol, 2) admission to the 8 hour observation area with initiation of the treatment protocol 3) direct admission to an inpatient department Education: staff were educated prior to implementing the program. Education included sensitivity training, information about the disease, pain management and other effective treatment interventions. Staff nurses also attended educational sessions to learn about complementary therapies for SCD including biofeedback, relaxation techniques and guided imagery. Procedure: Documents developed to treat patients in SCD crisis included an 8 hour admission protocol that was used in the ED or the observation area on the oncology department to rapidly treat a crisis. In addition to the standing orders, an 8 hour observation pathway was developed that focused on progression, assessments, possible precipitating factors, education for home management. Patient's perception of their care before and after implementation of the treatment program was assessed using two surveys. Both tools measured patient satisfaction using a 5-point Likert scale with responses ranging from 'very good' to 'very poor'. Higher scores indicated greater patient satisfaction. Patients who were admitted were placed on the SCD progression clinical pathway that had been in use for several years. After implementing the 8 hour treatment program in 1999, weekly team rounds were initiated to address challenging issues and situations related to the care of patients with SCD.
Comparison	Admission: Prior to establishing this treatment program, patient with SCD were placed on various departments of the hospital, but were most often admitted through the ED. Procedure: no other details reported
Length of follow up	Pre-intervention period: October 1997-September 1998 Post-intervention period: October 1999-September 2000
Location	USA

<table>
<tr><td>Outcomes measures</td><td>
Patient satisfaction: survey was conducted on 18 patients to evaluate patient responses on identified patient issues before and after implementing the treatment program. The survey results show that the new treatment program was effective in increasing patient satisfaction in the 4 areas the patients had identified as problematic.
<table>
<tr><th></th><th colspan="5">Before implementing treatment program</th><th colspan="5">After implementing treatment program</th></tr>
<tr><th>Patient issue</th><th>Very poor (%)</th><th>Poor (%)</th><th>Fair (%)</th><th>Good (%)</th><th>Very good (%)</th><th>Very poor (%)</th><th>Poor (%)</th><th>Fair (%)</th><th>Good (%)</th><th>Very good (%)</th></tr>
<tr><td>Getting patient medication on time</td><td>16.7</td><td>50</td><td>33.3</td><td>16.7</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>50</td><td>50</td></tr>
<tr><td>Knowledge of your disease and treatment</td><td>NR</td><td>50</td><td>33.3</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>66.7</td><td>33.3</td></tr>
<tr><td>Relationship with nursing staff</td><td>16.7</td><td>33.3</td><td>50</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>66.7</td><td>33.3</td></tr>
<tr><td>Emergency department experience</td><td>100</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>50</td><td>50</td></tr>
<tr><td>Overall satisfaction</td><td>16.7</td><td>66.7</td><td>16.6</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>NR</td><td>50</td><td>50</td></tr>
</table>
LOS and number of ED visits:
<table>
<tr><th></th><th>1 year before intervention (1998)</th><th>Following initiation of intervention (1999)</th><th>1 year post intervention (2000)</th></tr>
<tr><td>Average LOS</td><td>8.7</td><td>7.75</td><td>6.29</td></tr>
<tr><td>Average number of ED visits</td><td>73.5</td><td>22</td><td>9</td></tr>
</table>
</td></tr>
<tr><td>Authors' conclusion</td><td>This group of interventions resulted in significant improvements in length of stay, emergency department visits, cost per case and patient satisfaction.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>The survey tools used to assess patient satisfaction were evaluated by 5 healthcare professionals directly involved in the program development and they agreed that the questions accurately reflected patient satisfaction and were representative of areas of interest in evaluation. The paper reports that average LOS a few years before implementation of the new program increased to 12 days and there was a reduction in LOS before major changes were implemented. Therefore reductions may not be related to the implementation of the program.</td></tr>
</table>

Table 76 Evidence table for Mitchell et al (2002)

Bibliographic reference (Ref ID)	Mitchell et al 2002 (Ref ID: 1270)

<table>
<tr><td>Study type & aim</td><td>Before and after study/To improve the consistency and quality of care for patients with SCD</td></tr>
<tr><td>Number and characteristics of patients</td><td>N = 27 patients (In the 6 months before protocol implementation there were 235 visits to the ED, resulting in 76 admissions. In the 6 months after protocol implementation there were 188 visits to the ED, resulting in 46 admissions)
No other patient characteristics were reported.</td></tr>
<tr><td>Definitions</td><td>N/A</td></tr>
<tr><td>Intervention details</td><td>Admission/setting: Community hospital setting. If after 8 hours on the protocol in the ED, the patient's crisis has not been resolved, they are admitted to the designated medical-surgical unit for continued treatment.
Procedure: 'best practice' protocol about managing vaso-occlusive crisis was established based on literature search and common practice of pain centres across the country that treated a large volume of patients with SCD. Information about the protocol was communicated to the medical staff at medical staff meetings and through physician newsletter.
Education: As part of protocol implementation, the ED physicians and a core group of Internal Medicine (IM) and Family Practice (FP) physicians went through a credentialing process on the care of hospitalised sickle cell patients. This process involved attendance at an educational session on SCD, the use of titration of PCA medications, and instructions on the protocol. In addition, the ED nursing staff received in-service training on the use of the PCA pump. The protocol was implemented 6 months after the initial MEC approval had been given.
Healthcare professionals: Case manager was assigned to coordinate care for all sickle cell inpatients. The manager visits patients on the day of admission to discuss pain management protocol, patient's perception of their outpatient regimen and potential psychosocial issues that may have triggered their crisis.</td></tr>
<tr><td>Comparison</td><td>No specific details are reported but the paper focuses on process of care in the ED and hospital setting.</td></tr>
<tr><td>Length of follow up</td><td>Before protocol implementation: January-June 2000
After protocol implementation: July-December 2000</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures</td><td>Utilisation goal outcomes were assessed including patients treated and released, downgraded days and patients on protocol from ED through discharge. These outcomes are not reported in this evidence table.
Changes in utilisations averages:
<table>
<tr><th>Outcome</th><th>Before implementation</th><th>After implementation</th></tr>
<tr><td>Average LOS (days)</td><td>4.9</td><td>3.8</td></tr>
<tr><td>Number of admissions per patient</td><td>3.8</td><td>2.7</td></tr>
<tr><td>admission severity rating*</td><td>1.2</td><td>1.1</td></tr>
</table>
* based on patient's probability of death and measured by age, gender and clinical findings</td></tr>
<tr><td>Authors' conclusion</td><td>Outcomes, which were based on data from the 6 months before and after the protocol initiation, demonstrated an increased treat-and-release rate from the emergency department and a decreased average length of stay.</td></tr>
</table>

Source of funding	Not reported
Comments	N/A

Table 77 Evidence table for Montanez & Berland (2002)

Bibliographic reference (Ref ID)	Montanez and Berland 2002 (Ref ID: 8372)
Study type & aim	Before and after quality improvement project/To implement a clinical pathway for the treatment of sickle cell pain crisis and to evaluate its impact on practice processes and outcomes of care
Number and characteristics of patients	N = 144 patient (n = 64 pre-intervention, n = 55 during intervention, n = 25 post-intervention) No other patient characteristics were reported. Inclusion: all patients aged 18 years or older with a pain producing sickle haemaglobinopathy who were admitted to the ED or the inpatient medical services with pain crisis as the primary diagnosis. Exclusion: patients coded with a pain producing haemaglobinopathy but seen for a primary reason other than pain crisis or those who had a significant complication of sickling (e.g. acute chest syndrome) were excluded from the study
Definitions	Clinical and demographic data was collected using a standard questionnaire. Severe pain: prevents sleep/wakes at night; makes patient cry out/moan Moderate pain: very uncomfortable; stops usual activities Mild pain: uncomfortable, but relieved by home meds, can continue activities
Intervention details	Healthcare professionals: The pain team was a multidisciplinary group consisting of a pain specialist, a haematologist, a clinical pharmacologist and two internists. The pain team functioned as a case management team and participated actively in patients care. The team assessed adherence to the pathway and identified errors, deficiencies, attitudes and behaviours outside the objectives of the clinical pathway. They also prompted, educated and corrected medical personnel when appropriate as well as provided reinforcement and continuous feedback through monthly sessions, daily pain team work rounds and direct contact with specific personnel groups. The pain team was dissolved after the intervention period, but the members remained available for informal consultation and education. Procedure: The pain team developed an evidence based clinical pathway for the management of acute pain in general and for sickle cell haemaglobinopathy patients in particular. The aim was so that pain in and of itself was not the variable responsible for preventing the patients' discharge from the ED or the inpatient service. A 3 month period of dissemination and training was initiated following the development of the clinical pathway. Education: No specific details are reported but education was provided by the pain team.
Comparison	No other details were reported for pre-intervention settings.

<table>
<tr><td>Length of follow up</td><td>Pre-intervention: 64 patients were treated between 1st October 1997 and 30th April 1998 (7 months)
Intervention (pain team formed and pathway implemented): 55 patients treated between 1st October 1998 and 30th April 1999 (7 months)
Post-intervention: 25 patients treated between 1st February 2000 and 30th April 2000 (3 months)</td></tr>
<tr><td>Location</td><td>USA</td></tr>
<tr><td>Outcomes measures</td><td>Discharge: From the table below the percentage of patients discharged from the ED was 11% in the pre-intervention period, 27% in the intervention period and 40% in the post-intervention period.
Selected outcomes in study groups:
<table>
<tr><th>Outcome</th><th>Pre-intervention</th><th>Intervention</th><th>Post-intervention</th></tr>
<tr><td>Patients</td><td>64</td><td>55</td><td>25</td></tr>
<tr><td>Patients admitted</td><td>57</td><td>40</td><td>13</td></tr>
<tr><td>Uncomplicated admissions</td><td>56</td><td>40</td><td>13</td></tr>
<tr><td>Mean total LOS (days)</td><td>5.5 (range 1 to 17)</td><td>4.7 (range 1 to 14)</td><td>2.8* (range 1 to 5)</td></tr>
<tr><td>LOS ≤4 days (%)</td><td>43</td><td>62</td><td>92</td></tr>
<tr><td>LOS ≤2 days (%)</td><td>16</td><td>25</td><td>54</td></tr>
<tr><td colspan="4">Level of pain on day 2 (%)</td></tr>
<tr><td>Severe</td><td>23</td><td>17</td><td>8</td></tr>
<tr><td>Moderate</td><td>38</td><td>38</td><td>31</td></tr>
<tr><td>Mild</td><td>33</td><td>32</td><td>54</td></tr>
<tr><td>None</td><td>5</td><td>3</td><td>7</td></tr>
<tr><td>Mean time to relief (hour)</td><td>N/A</td><td>27.4</td><td>7**</td></tr>
</table>
*p = 0.05 for the comparison of LOS during intervention vs. post-intervention
**p < 0.08 for the comparison of mean hours to pain relief during intervention vs. post-intervention (calculation based on n = 29 intervention patients and n = 10 post-intervention patients for whom there were survey data)

Other outcomes reported include pathway adherence, medication used, route and discharges against medical advice which are not reported in this evidence table (see full paper for details). The paper also reports subgroup analysis of outcomes for patients who were on the pathway (n = 11), patients on pathway but there were errors in utilisation which were corrected with prompting (n = 11) patient who were on the pathway but the pathway was not followed (n = 1), patients not on the pathway (n = 17). These are not reported in this evidence table.</td></tr>
<tr><td>Authors' conclusion</td><td>The integration of a pathway, case management and education was effective in improving both the processes and outcomes of pain management for sickle cell patients</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
</table>

Comments	No patients were treated with hydroxyurea. A standard questionnaire that prompted the accumulation of relevant clinical and demographic information was completed prospectively for the intervention group (using chart and hospital information and patient interview). In the pre and post intervention groups, the questionnaires were completed retrospectively using hospital computer and chart reviews. The small size of the post-intervention group was a function of a shorter data collection period and lower rates of admission resulting in small numbers of inpatients. It was reported that the results were so striking that there was no more need to collect more patient data.

Table 78 Evidence table for Wright et al (2004)

Bibliographic reference (Ref ID)	Wright et al 2004 (Ref ID: 1042)
Study type & aim	Before and after study/ To reduce hospital admissions for uncomplicated sickle cell pain through offering day case pain management
Number and characteristics of patients	N = 440 episodes of severe pain in 89 patients over 5 years (2 years pre and 3 years post unit set up). No other patient characteristics were reported.
Definitions	Severe sickle cell pain: requiring parenteral opiates, unexplained on any other basis Single painful episode: attendances without a seven day break Failure of day care: hospital admission within 7 days of pain managed in centre Frequent attendees: Those in severe pain on 10 or more occasions per year
Intervention details	Day unit staff: three specialist nurses, half-time psychologist, nursing auxiliary and receptionist. Access to a social worker on a sessional basis. Haematology staff from the hospital provides medical cover. An additional consultant haematologist has been funded as part of the development. Nursing staff trained to cannulate and bleed Admission: Centre accepts self-referrals and referrals from primary care and casualty Pain management protocol: assessed by specialist nursing staff using standardised pathway. In the absence of contraindications (temperature >38, respiratory signs/symptoms etc.) the specialist nursing staff may administer a maximum of two doses of parenteral opiate analgesia according to established individualised protocol. Monitoring: pain control is reviewed regularly and linear pain analogue scores recorded. Medical review is performed after arrival in the centre. Discharge: On discharge, a small supply of oral opiate analgesics and anti-inflammatory agents are provided and centre specialist nurses perform follow-up (telephone or home visit) until crisis settles.
Comparison	Pre-unit conditions not reported
Length of follow up	2 years before unit set up and 3 years after unit was set up
Location	UK

<table>
<tr><td>Outcomes measures</td><td>Table 1-Changing pattern of admission and usage over a 5 year study period (2 years prior to set up and 3 years after)
<table>
<tr><th></th><th>01/07/1998-30/06/1999</th><th>01/07/1999-30/06/2000</th><th>01/07/2000-30/06/2001</th><th>01/07/2001-30/06/2002</th><th>01/07/2002-30/06/2003</th></tr>
<tr><td>Number of patients</td><td>141</td><td>139</td><td>not available</td><td>209</td><td>235</td></tr>
<tr><td>Hospital admissions</td><td>207</td><td>205</td><td>126</td><td>123</td><td>104</td></tr>
<tr><td>Number of patients (% of population)</td><td>29 (21)</td><td>38 (27)</td><td>41 (not known)</td><td>46 (22)</td><td>54 (23)</td></tr>
<tr><td>Bed days (median duration of admission)</td><td>1662 (6.0)</td><td>1651 (6.0)</td><td>851 (6.5)</td><td>1069 (6.0)</td><td>636 (6.5)</td></tr>
</table>
The centre has managed 440 episodes of severe pain in 89 patients over 677 visits. Over the 36 month period there have been 116 admissions in 44 patients following failure of day case management. 46 admissions occurred in the first year, 31 in year 2 and 34 in year 3.</td></tr>
<tr><td>Authors' conclusion</td><td>A centre offering day case management of painful crises reduced unnecessary hospital admissions for uncomplicated pain.</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Comments</td><td>None</td></tr>
</table>

Review question 5: Information and support needs of patients and their carers during an acute painful sickle cell episode

Table 79 Evidence table for Alleyne & Thomas (1994)

Study ID	Alleyne & Thomas (1994) Ref ID: 2158
Aim	To examine the experience of pain management from the perspective of individuals who have required hospitalisation for painful crises and the perspective of nurses responsible for their care
Theoretical approach	Methodological influences were: The new paradigm: (Reason & Rowan, 1981) A collaborative approach between experimenter and participants from initial formulation of the research question to overall conclusions of the research

	The feminist methodology (Webb, 1991) Based upon a reflective and liberative paradigm, valuing subjectivity, collaboration and action Theoretical approach was assumed to be dependent on content analysis.
Data collection	A qualitative design was employed using in depth semi-structured interviews. The interviews were carried out through both group discussions (lasting 2 hours) and individual interviews (lasting 45 min). Guided conversations facilitated the group discussion. Ethical approval was obtained from the local ethics committee. All information was kept confidential – participants were referred to by allocated number only. Taped interviews were destroyed at the end of the study.
Method & process of analysis	All interviews were audio-taped, transcribed verbatim and typed up after each interview Content analysis identified categories and codes were ascribed to relevant categories within the data. Quotations were used in the study write up to augment key themes for analysis Information was typed soon after each interview. Patients and nurses were given copies of transcripts and reviewed the information for accuracy. The content was analysed (not stated by whom/how many) to ascribe labels through a process of coding themes. This included themes which were common to both patients and nurses.
Population & sample collection	The patient population included 10 adult patients (8 female, 2 male, all Afro-Caribbean origin) All patients were recruited from the sickle cell support group meetings held by the hospital in which the study was located. 10 female nurses were recruited from the haematology ward. Both day and night duty staff were recruited.
Key themes	The key findings considered the experiences of both patients and nurses. Four categories recorded specifically related to both patients and nurses experiences. The fifth category 'playing up' relates solely to the experience of nurses: <u>Poor pain management:</u> This category examined the patients' experience of pain assessment and ability to obtain analgesics. It also described nurses' responses to the patients' pain. The following subcategories were identified <u>Difficulty in obtaining pain killers:</u> Patients described instances whereby they had to demand painkillers when needed and had to wait for up to half an hour for analgesics to be provided. "You can wait up to half an hour" (P1) "Even longer than half an hour, and even after they have been to see you, you wait another half an hour more"(P2). Lack of monitoring of pain severity: Few patients (n=2) had ever experienced nurses to attempt to assess the severity of their pain and this was generally performed by the more inexperienced nurse. "Sometimes you find it's the trainees" (P6) "I must admit there are a couple of nurses, they ask you and I must admit, it was culture shock" (P8)

	Lack of sympathy and explanation: All patients provided examples where nurses seemed to be unsympathetic to the patients' needs "Some of them especially on [ward] they're not sympathetic, they'll say 'You'll have to wait, I've only one pair of hands' sort of attitude" (P3) One participant reported they rarely provided explanations for delays. "They never say 'We're very busy' or 'You'll have to wait because we've only X amount of staff" (P9) Nurses' doubts about genuine nature of pain: Most patients (n=8) described situations where nurses doubted the patients' pain status and subsequent request for analgesia. "You get things like 'Didn't we just give you something, are you sure you're due?'" (P8) "Or you get do you really need it?" (P4) "You know they make you feel guilty like you're doing something wrong" (P3) Deliberate delays in provision of analgesia: Most patients reported that nurses seemed to delay providing analgesia because they misinterpreted patients' requests as 'drug seeking behaviour'. "I've got the feeling that some of them purposely prolong it" (P6) "They don't realise that while they're prolonging it, the pain's getting worse, and it's stressful" (P4) Half of the nurses confirmed that deliberate delays took place because they had witnessed colleagues doing it. One nurse reported that she usually informed patients' if there was a delay "I always try when they've asked for analgesia and they're not due for 10 minutes to say I'll just do this one and come back, I take the chart with me" (N2) Nurses' anxieties about their own abilities: All nurses seemed to be anxious about their own abilities to control effectively. One nurse described it as 'trial and error'. Anxieties about pethidine: The study found that pethidine was the most commonly used analgesic during a SC crisis. The patients sample expressed a preference for it but also reported that it was very hard to obtain unless you were 'rolling around in agony'. Few nurses (n=2) reported that other nursing colleagues were reluctant to administer pethidine because of patients' behaviour prior to their request. "We see patients laughing and joking one minute, or watching television, and then they want pethidine" (N4) All nurses expressed concerns for the prolonged use of pethidine "I think it's a big problem, it's expensive, time consuming, it takes two nurses to check, it's a controlled drug, so it has addictive qualities and nurses know this" (N6) The majority (n=8) had little knowledge about Pethidine's dangerous side effects. Lack or loss of control: This category included descriptions where patients and nurses feel out of control and helpless. Nurses felt that doctors had a dominant influence over nurses because they controlled the prescription of analgesia. Patients were concerned about their lack of involvement in their own pain control, especially when doctors reduced the amount of pethidine they were receiving. They felt they had to justify the amount of pain relief (pethidine) they required. "I've found that doctors are very quick, they say, 'let's have a look at how much pethidine you're having, what about reducing it to 50?' You have to say 'No, I'm still in a lot of pain'. We're old enough to know how much pain we're in" (P10)

	Patients stated their preference for and satisfaction with a route of administration via continuous IV infusion. They thought this was an effective way to control pain. Nurses, however, thought it was an unsatisfactory route of administration because patients would 'fiddle' with the drips and pump. "We stopped using the infusion because they fiddle with the drips, and they quickly caught on to fiddle with the Imed (Infusion pumps)" (N6) Two nurses thought patients could not be trusted to be responsible using patient controlled analgesia (PCA) "It would be interesting to see the effects when control is given over to them, but you are going to get those who are sensible, and those who abuse it, you know, want the maximum and we have no control over it" (N1) Lack of individualised care: All patients described their experience of care as not being treated as individuals. They believed nurses treated all SC patients as a stigmatised group that were branded as 'sicklers'. Nurses were frustrated at their inability to individualise care. "You're meant to treat them as individuals, but when you go in a bay and there are four of them in, you can't say 'Do you want pethidine as well'?" (N5) Night nurses also reported that other nurses did not treat patients as individuals. The nursing staff reported that other nurses can become suspicious about pain because they could not see physical evidence that the patient was experiencing pain. "...I think it's because you can't see any physical evidence they [nurses] get suspicious" (N9 and N10) Playing up: This theme emerged from the nurses accounts of experience with patients with sickle cell disease. Nurses described patients requests for analgesia as 'playing up' and patients thought their regular requests for analgesia were a burden on staff because it could increase the nurses' workload. "Patients are dependent on nursing staff for pain control and fluids I don't believe they deliberately antagonise the nurses" (N8)
Source of funding	Not reported
Limitations	The specific role of the researcher or their relationship to participants was not reported in the study. It is unclear how this lack of reflexivity impacts upon the validity of the method Number of researchers involved in coding of themes was not reported– it is therefore unclear how reliable data analysis was Data analysis could have been more detailed by providing more in depth consideration for the circumstances in which reviewed experiences were considered
Comment	UK Study (based at an inner London district hospital), focuses strongly upon administration of pethidine as the main method of pain management and included adults only.

Table 80 Evidence table for Booker et al (2006)

Study ID	Booker et al (2006) Ref ID: 746
Aim	To gain a greater understanding of the barriers faced by SCD patients in managing pain and perceptions of treatment SCD patients receive from healthcare professionals. To investigate how service users (patients) manage their pain. To investigate patients' understanding of physicians' prescribing decisions & evaluate the bi-directional flow of information between patients' and

	physicians'. To highlight areas where service users (patients) believe pain management strategy is not ideal. To explore the issues patients perceive as important in acute crisis pain management and evaluate if healthcare resources are targeted to address these issues.
Theoretical approach	Thematic analysis
Data collection	A qualitative design was used incorporating a focus group methodology. This was used to investigate patient understanding of treatment decisions and pain management strategies for patients experiencing a painful SCD crisis. Prior to conducting the focus group the researchers conducted a 3-month pilot observing consultations, in order to identify and understand pain-related topics that were frequently raised by patients during consultations. Field notes taken during the observations were coded for themes. This identified 13 recurrent topic areas. Semi structured stimulus material was based upon these pain related topic themes. Open-ended questions were constructed from this stimulus material and used as grounding for discussion. All focus groups lasted for 1 hr. A moderator used the open-ended questions to facilitate discussion. A second investigator recorded field notes of non-verbal communication. The same introductory statement was used at the start of each session and a debriefing session was conducted following the end of the session. Key themes from the focus groups were noted at that time.
Method & process of analysis	All focus groups were audio taped and transcribed verbatim. Two investigators were involved in transcription and data was checked twice for accuracy. No a priori hypothesis was made regarding the research content and all data was analysed using constant comparative methodology. <u>Thematic analysis was used to identify three coding tiers:</u> Open coding (basic themes), Axial coding (group related issues) Selective coding (upon saturation). Field notes were used to annotate transcripts and to identify key aspects of non-verbal communication Once analysed the key themes were discussed with representatives of focus groups to ensure findings were a true representation of discussion.
Population & sample collection	All participants were randomly selected from a list of eligible participants that had previously been treated as inpatients at the SC centre to take part in one of four focus group sessions. Purposive samples were determined by quota allocation to ensure a representative balance of ages and genders. Both frequent day-unit users and infrequent consulters (attending only for annual follow up were eligible). This was to gain a spectrum of service reliance within the sample. All participants had previously been treated as inpatients in the centre. All participants were regular attendants of outpatient appointments but not all were current regular service users. Twenty participants were selected at random (10 participants took part; mean age 32 years, range 22-53, 8 Afro Caribbean, 1 Portuguese, 1 African origin).
Key themes	In the most part the identified themes were discrete, but there was some overlap of topic areas within each theme. The three identified themes were:

	Fear: This was a recurrent theme throughout. Participants contextualised responses in relation to fear of loss, physical or social capability and fear of people or life. These included: Death: Participants were fearful of an early death due to the complications of SCD. Participants commented that sometimes the pain was so bad that death was the only release. Uselessness: Participants were unable to complete activities of daily living (ADL- looking after themselves) when they were in acute pain. Comments included finding it hard to 'do the most basic things' and participants felt useless as a result. Helplessness: Participants felt helpless due to disabling nature of pain. One participant felt reliance upon his wife for assistance undermined his adult status, left him feeling like a child and contributed to feelings of helplessness. Isolation: Two distinct aspects emerged: Feelings of fearful isolation meant that only SCD patients themselves understand the extent of pain. Healthcare professionals cannot understand it. Feelings of social isolation included being separate from others. Participation in pain management focus groups held at the centre helped patients to overcome the feeling of being socially isolated. It was also recognised that feelings of isolation may drive maladaptive coping responses and restrict quality of life. If patients feel mistrusted or stigmatised by healthcare workers, this can manifest in hostility towards healthcare professionals or active avoidance of service use. Coping: All participants had lived with SCD for many years and therefore had developed their own coping strategies. The following themes emerged: Nature of pain and strategies: All focus group participants recognised that the sudden onset of pain was difficult to deal with. SCD pain was experienced on a continuum from mild to severe throughout the crisis. Participants would use different management strategies depending on the severity. Faith: Participants had faith in medical services: "When I come to hospital, like my mind tell me- says I am going to get better- I am in a safe place" (P1 G1) Medication: A strong emphasis was placed upon worries about overdosing, concerns about high levels of analgesia and the long term effects that medication dependence might have. Medication use varied depending on severity of pain (ranging from non-prescription pain killers for non-severe pain to medication that could only be obtained in hospital setting). Some participants found it was difficult to obtain painkillers from healthcare professionals Anger: Participants' anger and frustration would manifest in anger in the pain and failure of medication, anger at oneself, anger at those around and anger at healthcare professionals: "You are taking more pills and it doesn't work and you take another one and it doesn't work, and you start to feel angry at just why it doesn't work ... and you say to the doctor 'this is not working, you know?'... and you get frustrated at others!" (P4 G2) Interacting with others: This theme included peer and family support and communication with healthcare professionals Support from others: Participants relied heavily upon a select group of family and friends to assist with their personal support Communication with healthcare professionals: Some participants likened dealing with healthcare professionals to a battle. They felt they had to work hard to try to convince their doctors that they were in genuine pain. Participants were likely to avoid consulting with their doctor when they were in crisis to avoid being labelled as opioid dependent.

	"So sometimes you fight it within yourself. You don't want to go and ask for help because you know what they are going to do....you know what it's going to be like when you go to A&E- you think 'oh, no'!"(P8 G3) Many participants felt as though doctors did not have sufficient knowledge of sickle cell disease to be able to make valid treatment decisions. "...You supposed to be a doctor if you are studying about sickle cell you should know- you should at least have the basics" (P6 G2)
Source of funding	Not reported
Limitations	Full and clear reporting of theoretical approach, data collection, validity of qualitative methodology and data analysis providing a thorough outline of the study
Comment	UK study – based at SCAT centre in Birmingham City Hospital Adults only

Table 81 Evidence table for Johnson (2003)

Study ID	Johnson (2003) Ref ID: 1248
Aim	To collect data regarding patients' perceptions of using Patient controlled analgesia (PCA) for Sickle cell disease (SCD) from those who have and those who have not previously experienced using PCA. To explore the scope for improving patients' perceptions of PCA To devise a strategy to improve the delivery of analgesia through PCA
Theoretical approach	Not reported
Data collection	A mixed design using both questionnaire and qualitative methodology (focus group) was employed. Data was obtained from both SCD patients that have previously, and those that have not used PCA. Initial fieldwork was carried out to explore patients' reactions and awareness of PCA. A questionnaire was devised following an initial pilot with 5 participants. The pilot identified where administration of the instrument could be modified. The questionnaire was used as the principal data collection tool. The questionnaire was administered to eligible patients. Response rate was 88% The questionnaire was based upon emerging concepts and included both forced choice (multiple choice) and open-ended questions. Multiple choice questions were designed to encourage participation and ease coding of responses. To check consistency key information was obtained from multiple questions. Most questionnaires were pre-coded and open ended questions were also used to allow for unprompted responses. The questionnaire instrument was approved by the local ethics committee. A focus group was also conducted with 5 volunteers from the participant sample. Sampling for the focus group was not reported. The focus group was based upon the key themes obtained from participants' response to open-ended questions in the questionnaire and was used to clarify ambiguities resulting from the questionnaire data. The procedure followed in conducting the focus group was not reported in detail. Field notes of non-verbal behaviour were obtained to supplement the discussion notes. All discussion points were audio taped and transcribed. Demographic data was also collected.

Method & process of analysis	Documentary data and responses to closed questions from the questionnaire were coded. Data obtained from the open ended questions was analysed using ethnographic analysis (based on direct quotations) and content analysis. Categories were identified and these were systematically verified through cross-referencing to the underpinning objective of each question. Data from the focus group was categorised using a process of standardising, unitising and recording. The entire transcript was scanned for recurring themes. The number of coders and reviewers involved in data analysis was not reported in the study write up.
Population & sample collection	All consenting adult SCD patients who were admitted to the hospital during the study period were eligible to complete the questionnaire. Patients who were thought to be too unwell were not approached to participate. 40 participants (representing 87% of all possible respondents) completed the questionnaire. These included 18 male, 22 female, (aged 18-49 years). 83% were admitted for acute pain management. Five participants took part in the focus group. These participants were identified from the modal age bracket.
Key themes	<u>Pain relief experience</u> 95% receive diamorphine injection as pain relief, 90% received pethidine injection, 65% had used PCA and 60% of respondents had used a combination of all three pain management modalities. All patients had previous opioid experience for acute pain. All (except one) were receiving opioids at this admission. There was a trend towards the use of diamorphine – 60% were currently receiving it via PCA or nurse administered injections. <u>Efficacy of various pain management modalities:</u> Data was obtained from patients who had prior experience of different pain management methods. Data obtained from the questionnaire found that pethidine was judged the most effective drug (on an effectiveness scale of 0-5 it received a modal score of 4). Five patients had incurred seizures using pethidine. Diamorphine and PCA received a score of 3 on the effectiveness scale. Diamorphine was preferred because the side-effects were more tolerable. Ten patients said that diamorphine was the only analgesic they could tolerate. 29% favoured PCA. Their reasons centred on its potential to provide instantaneous relief, level of control over their pain and its effectiveness. Other reasons for favouring PCA focused upon its potential to reduce anxiety and confrontation arising from serious analgesic requests. Data obtained from the focus group found that PCAs effectiveness was dependent on dose and frequency of administration. Two participants thought small doses delivered at short intervals were ineffective and used PCA only in a regimen mirroring nurse administered injections. All five participants included in the focus group preferred another modality especially during the early part of a 'really bad crisis'. <u>Control:</u> 62% of patients with PCA experience thought PCA allowed patients to have more control over pain relief than other modalities. Seventeen comments related to PCAs potential to promote timely pain relief. Some participants thought PCA helped to improve pain tolerance because of the predictability of dose delivery. One patient thought PCA had the potential to avert long delays in emergency departments. <u>Patient-Staff relationships:</u> Data from the questionnaire found that 88% of experienced PCA users thought PCA gave greater freedom from staff but this was not always an

	advantage. Two respondents thought greater freedom was advantageous through less staff-patient confrontation. Over half of the participants (mostly experienced PCA users) thought the reduced time nurses spent with patients was disadvantageous. PCA was described as 'convenient for staff' and 'led to non-existent nursing care'. Data obtained from the focus groups supported the findings of the questionnaire. Participants described situations where nurses were skimping on patients – regardless of modality. Where PCA was used, the participants thought nurses were inclined to focus attention on the machine and not on the patient. <u>Choice:</u> 40% of experienced PCA users thought they had been coerced to use PCA at least once. In those participants that had never used PCA, 75% stated they had never been offered it. Data from the focus group indicated that the way in which PCA was offered was inconsistent and was dependent on staff preferences. Patients generally do not feel involved in dosing decisions about their analgesia. <u>Technology:</u> 60% of patients highlighted issues relating to functionality of PCA. Two patients thought the pumps were cumbersome and reduced mobility unacceptably. Three patients stated they would have selected PCA over diamorphine injections if more portable machines had been available. Issues also reported around malfunctions associated with PCA use (e.g., the PCA alarms activated frequently). <u>Cannulae:</u> Two thirds of patients with previous experience of PCA and all focus group participants cited problems (such as site infections and irritations) following the indwelling cannulae associated with PCA. Other issues included scarring and leakages.
Source of funding	Not reported
Limitations	The role of the researcher has not been described in detail. This lack of reflexivity could have an impact upon the validity of the focus group methodology Unclear how reliable the analysis was- although the method of coding was described, cross-referencing and inter-rater assessment has not been reported Context bias has not been adequately considered in describing the settings Data analysis could have been more in depth (the data obtained from the focus groups was only summarised - without any elaboration or provision of quotes to augment the findings).
Comment	Single centre study Adult population Based in UK

Table 82 Evidence table for Maxwell et al (1999)

Study ID	Maxwell et al (1999) Ref ID: 3523
Aim	To investigate how socio-cultural factors influence the management of sickle cell disease by comparing experiences of pain and pain management in SCD patients who had different frequencies of hospital admissions for management of their pain.
Theoretical approach	Not reported
Data collection	A mixed design was employed using qualitative data from semi structured interviews and focus groups and a structured questionnaire to identify patient demographic characteristics and current treatment. Focus groups and semi structured interviews were the main methods used. All participants completed a structured questionnaire to collect socio demographic data, information about haemoglobin status, usual analgesic drugs and current treatment. Eighteen semi structured interviews were conducted with 15 participants. The participant chose the setting. Six pilot interviews were initially used to develop the topic guide to be used for the focus group. Ten interviews were conducted in parallel with the focus group sessions (for patients who were in hospital but were unable to attend the focus group). Focus group discussions were based upon responses to questionnaire. Participants were allocated to one of eight focus group sessions which met for two discussions (lasting 1½- 2½ hours). Discussions included: diagnosis, child and adulthood experiences of pain, hospital experiences, primary care, analgesia, anatomy of a crisis, employment and education, support and relationships and identity and lifestyle. One facilitator attended the focus group and introduced the topics, asked questions and encouraged participation of all group members. The paper does not report sufficiently which methods were used to introduce topics to participants to maintain consistency across all groups
Method & process of analysis	Quantitative questionnaires were analysed using statistical software (Epi-Info v6). All qualitative data was professionally transcribed by an external source. The transcripts were then checked for accuracy, against original recordings, by the main researcher. Non-verbal items (such as laughter or murmurs were also included checked against the transcript. Nud*ist software was used to assess qualitative findings. Coding categories were developed from the data rather than relying on a predetermined analytical framework. Text units (uninterrupted speech) were grouped according to common themes. The general themes were then subdivided into further themes as analysis of the data progressed.
Population & sample collection	Theoretical sampling (a non-random sampling of participants with specific characteristics selected to aid the development of theory) was used to recruit participants with sickle cell disease across the Greater London area. Various channels were used to recruit participants (researcher visiting inpatients, referral by specialist, snowballing, participation in previous research and researcher visiting outpatient clinics). 57 participants with SCD were recruited. These included the following: Participants with HbSS or H-β thalassaemia (n=44), HBSC (n=7), unknown (n=4). All participants were aged 20-60 years (mean age 34 years). 40 participants took part in the focus groups, 6 participants took part in both interviews and focus groups, 9 participants were interviewed only. Participants were allocated to the focus groups depending upon the information they had provided in their questionnaires. Each group composition was determined by ethnic origin (Afro Caribbean or West African), sex and number of times they had been admitted to hospital in the previous year (>3 or <1).

Key themes

Questionnaire results

Patients admitted infrequently were less likely to use strong opioids and more likely to use mild analgesics in hospital. All patients admitted three or more times to hospital had required strong opioids compared to only 72% in those admitted fewer than three times (95% CI of difference in group proportions 10% to 46%). Table 1 shows there was considerable overlap in the number of painful episodes between those admitted frequently and those who manage pain at home. Half of those who had managed pain at home experienced 10 or more painful episodes during the previous 2 years.

Table 1: Haemoglobin status and treatment in the hospital by number of hospital admissions per year.

Variable	**Participants (n=57)***	**Hospital admissions per year**	
		3 or more (n=28)	**1 or fewer (n=29)**
Haemoglobin status			
SS or S/β-thal	44 (77)	24 (42)	20 (35)
SC	9 (16)	4 (7)	5 (9)
Unknown	4 (7)	0	4 (7)
Transfusions & hydroxyurea			
Transfusion ever	43 (75)	19 (33)	24 42)
Transfusion regimen currently	4 (7)	4 (7)	0
Using hydroxyurea	5 (9)	5 (9)	0
Missing data	5 (9)	0	5 (9)
Usual drugs taken in hospital			
Strong analgesia (pethidine, diamorphine, morphine or combination)	45 (79)	27 (47)	18 (32)
Non strong analgesia (no pethidine, diamorphine, morphine or combination)	7 (12)	0	7 (12)
Missing data	5 (9)	1 (2)	4 (7)
Number of self-reported painful episodes in previous 2 years			
1-2	2 (4)	0	2 (4)
3-10	17 (30)	5 (9)	12 (21)
11-20	12 (21)	4 (7)	8 (14)
21-30	8 (14)	4 (7)	4 (7)
>30	13 (23)	11 (19)	2 (4)
Missing data	5 (9)	4 (7)	1 (2)

*values are number (percentages). Painful episodes do not add up to 100% because of rounding

	Qualitative results focused on two main themes: Experiences of hospital care and strategies for management of pain. Focus group data found that the two areas were closely linked: patients' experiences and satisfaction with pain management was closely associated to their hospital experiences. This was augmented by the attitudes and behaviour of their associations with hospital care-workers. Patient experiences of treatment while in hospital Mistrust: Participants gave accounts of feelings of mistrust by their professional caregivers towards them. All of the participants in the groups that were frequently admitted to hospital and two of the groups who usually managed pain at home described being suspected by healthcare professionals of exaggerating pain. "The doctor will look at you and he goes 'I don't think you're in a lot of pain'" (focus group 1). This was contrasted with some participants used to managing pain at home who described how healthcare professionals suspected them of understating the amount of pain. "They get suspicious because they can't believe you can be better in 2 days, but if I can look after myself, I don't see why I should be there... I feel better, I can stop taking [the painkillers].... Once I didn't have [any] more pain but they [were] giving me tablets which I didn't know were painkillers" (focus group 7) Stigmatization: A prominent theme throughout the focus groups and interviews was that patients with SCD perceived they were treated differently from other in-patients. Virtually all participants thought that patients were stigmatised as drug addicts "The nurse turned around to me and said 'It's not that we [don't] want to] give you the painkillers it's [because] we're scared that you're [going to] get hooked on it ...'" (focus group 3). Control: Participants described instances where hospital caregivers regularly exerted control over care regimes and would not include patients in decision-making, especially relating to giving drugs (including over treatment and under treatment of pain, hospital admissions and discharge). P "They try to give me diamorphine [diacetylmorphine hydrochloride] but I try to take as small [an amount] as I can... sometimes they push" I "They want you to take more?" P "Yes, they keep saying to me 'Oh, the pain will come again' And I say 'When the pain comes, I will tell you" (focus group 7) "You do find certain nurses tend to overstep their bounds.... they feel you should be having less than .... on the prescription ... and they will try and control your pain regime[n] to the way they think it should go" (focus group 2) "They kept saying 'I think we're going to send you home', and yet I knew it was the sort of chest pain that I should be in ....So there was this debate ... in the end I was right, it was sickle lung" (focus group 5) Neglect: Participants reported the neglect of various needs: including personal care and monitoring of vital signs. Some patients described this as evidence that patients with SCD were a low priority for health professionals. Failure to provide adequate psychosocial support while on the ward was also raised. "The nurses just seem to concentrate on the pethidine injections and that's it. I've been in days without having any assistance with my hygiene and personal needs and changing sheets and helping me with fluids..." (from an interview) "On [names ward], observations wasn't done ...if they come around and you're asleep they leave you... Sometimes they've already written in what your

	temperature is, but the thermometer is still under your arm" (from an interview). Strategies for pain management and treatment seeking: In-hospital experiences and self-management pain strategies of patients who usually managed their pain at home were markedly different to the strategies used by patients who were frequently admitted to hospital: Patients used to managing pain at home: This group of patients revealed a more sophisticated appraisal of hospital services. They demonstrated a strong sense of self responsibility for managing their condition. They were able to assert their ability to influence their own pain management regimes. They acknowledged that nurses or healthcare workers were not likely to fully understand treatment needs of patients with SCD and therefore relied on their ability to self–educate themselves about SCD pain management strategies and they were more likely to resist admission to hospital. "I think you do have to educate yourself because you'll be in wards where nurses have never seen a sickler- it didn't come up in their training – so I think it really comes down to you at the end of the day" (focus group 6) Patients frequently admitted to hospital: This group of participants advocated the importance of developing relationships with healthcare workers so that they had experience and knowledge of how the patients' crisis presented, and the most appropriate pain management methods patients used. "If you're in a regular hospital where they know you... they tend to build up some form of relationship because they've seen you before. So they know exactly how your crisis behaves, how you usually cope. They can work with you" (focus group 1). They were likely to use multiple hospitals. If care was not sufficient in one hospital they would discharge to use an alternative hospital. Some patients were likely to act either aggressively or passively in response to caregiver pain management requests.
Source of funding	The King's Fund and Marks & Spence
Limitations	The role of the researcher (in conducting the interviews) has not been clearly reported- a lack of reflexivity could influence the validity of the qualitative approach Context bias has not been adequately considered in the reporting of the interview settings
Comment	UK study Adults only

Table 83 Evidence table for Maxwell & Streetly (1998)

Study ID	Maxwell & Streetly (1998) based on Ref ID: 1745 (NB: this was an abstract only) original report obtained from the Sickle Cell Society- this research was the pilot for Maxwell et al (1999)
Aim	To investigate the issue of sickle cell pain and pain management from the patients' perspective To consider the experiences of patients that usually manage pain at home alongside those who were moderately and frequently admitted to hospital
Theoretical approach	Not reported
Data collection	Focus group discussions and individual interviews were the main methods used in the research. Demographic data was collected as described in Maxwell et al (1999).

	Six pilot interviews were conducted as described in Maxwell et al (1999). Participants chose the interview site, four chose local SC centre, two chose their own home. Nine additional interviews were conducted (as reported in Maxwell et al, 1999). These interviews were conducted in hospital- usually in private rooms, although a few preferred to be interviewed at their bedside. The researcher made two visits to complete the interview and had developed an on-going relationship with the participants. Focus group discussions were as reported in Maxwell et al (1999). The focus groups were conducted in two premises (London voluntary sector resource centre and UMDS Primary care skills centre) The main themes discussed during the interviews and focus groups included: Diagnosis; Childhood experiences of pain; General pain experiences; Hospital experiences; Admissions; Discharge; Primary care; Analgesia; Anatomy of a crisis.
Method & process of analysis	As described in Maxwell et al (1999).
Population & sample collection	As described in Maxwell et al (1999).
Key themes	Key themes explored the differences between those who usually managed pain at home with experiences of those who were admitted to hospital: <u>Family knowledge, attitudes and behaviour:</u> Some patients reported that within their home life their parents had been confident to manage pain and decide when hospital care was necessary. Others reported that their parents had received little information or support from health professionals. These parents were urged to bring their child into hospital at the first sign of pain "If I was in real pain, she would phone the ambulance and say it's an emergency and I would go straight in....the majority of the time she wouldn't call the GP if I was in pain, she'd call an ambulance straight away" (interview 1) They relied heavily on hospital care and were not confident in challenging medical authority "I didn't go into hospital until after eleven years old when my GP sent a letter to the hospital saying he wanted me to be seen by a specialist and [we] saw a consultant and she said 'Any time he has any more pains just call this number... bring him straight here to hospital'.... then from there, after eleven years old I remember going into hospital quite frequently" (interview 1) <u>Child involvement in managing condition:</u> Participants varied in the extent to which they were involved in making decisions about their condition as children: Participants that usually managed pain at home were more likely to be involved in decision making from an early age. "It depends on me. My parents took me to hospital when I said.... they asked me do I want to go to hospital, is it hurting that much More frequent admitters were less likely to be involved in their decision making when they were children "...My mother would always say 'Are you sure you should go in?' I'd say, 'Well, no mum, I can cope with it at home', but she'd still always tell me 'Well I think you should go into hospital'" (focus group 2.1) <u>Responses to pain:</u> <u>Self-responsibility for pain management:</u> Home pain managers were likely to take self-responsibility for pain management. They had a strong sense of personal responsibility for managing pain because they were taught to safely manage their condition at home "... All that doctors can do is give you tablets, but it's up to you too, you know, so personally I think I'm responsible for the management of my pain. And I usually tell the doctors also what I want, not what they want, so I think I'm in control" (focus group 7.2)

	Moderate admitters were capable of taking responsibility for pain management while at home, but believed their self-responsibility was limited by the power of health care professionals to take responsibility for pain management while in hospital. I: "Who do you think is responsible for managing your pain?" P: "While I'm at home I am. When I'm in the hospital the doctors are". (Interview 2) A small number of patients frequently admitted felt they had a lack of responsibility for their own pain management and relied totally on healthcare professionals. I: "When you're in hospital, do you feel that you're actively involved in your pain management?" P: "No." I: "Not at all? Do you think that it's totally other people making the decisions?" P:"Yeah, yeah, yeah" (Interview 10) <u>Mental strategies</u>: Participants that usually managed pain at home would have more sophisticated ways of conceptualising pain .They believed that their state of mind and cognitive techniques could help them manage their pain. "Think about how you overcame the last crisis....Take control of it. Just try to think 'I can deal with it' and try to be brave enough to actually stand up to it....Just keep concentrating on it, you know, internally. Sometimes it does work. I think 'I'm doing wonderful, I'm doing well', and if I think that then it's going to go away sooner or later. Sometimes it works, sometimes it doesn't" (focus group 8.2) Participants who were moderately admitted would use distraction as a response to pain. This group were less likely to use sophisticated measures and expressed less confidence than participants used to managing pain at home in their ability to control their pain. "You only think about pain when you are sitting down or when you are trying to get to sleep but if you are walking around, you are talking with people you can tend to forget about the pain and ignore it" (focus group 4.1). The most frequent admitters identified an irrelevance of using mental techniques in responding to pain. "I tend to concentrate on my pain and I can't... I can't be distracted no matter how much I try or anybody else tries, once I have pain, my whole focus, my whole attention, everything is on that pain...I fell that pain. Like I'm living it everywhere" (Interview 11). <u>Attitudes towards services:</u> <u>Resistance:</u> Attitudes of participants who usually managed pain at home were more likely to have a critical attitude to hospital services and believed that hospital admission was not in their best interest. They expressed a determination to take responsibility for their condition by managing their pain at home. "Well I think you have to nowadays start taking more control over yourself, you know, otherwise they just walk all over you. Send you in and out of hospital and do a Trans Ex [exchange transfusion] here and you wouldn't know what was going on" (focus group 7.2). <u>Relationships:</u> Attitudes of frequent admitters showed that participants tried to develop long-term relationships with their hospital carers in order to receive more individualised care. "I've just stuck with [hospital], they know me there, the consultants and admissions and day ward and I mean, at least I negotiate my care" (focus group 3.1). <u>Aggression:</u> A small minority of patients who were frequently admitted would use verbal or physical aggression if their pain was under-treated, or they were frustrated with their inability to communicate effectively with their healthcare professionals. "Every day I come to casualty he [the junior doctor] will send me home... one day...he cancelled my painkillers and said I would have to go home, and I

	said ‘Today I’m not going home’.... So I held him and I punched him” (Interview 12.1). Passivity: Some frequently admitted patients would develop a passive approach to their care- relying on healthcare professionals’ judgement to provide pain control. “Whenever they [the doctors and nurses] say anything to me that I don’t like I just let it go by.... Whatever they want to do, they can just do it to me” (Interview 10). Experiences of hospital care: Positive experiences: A minority of patients in all groups identified positive experiences. These were related to the following factors: If patients had established a long-term relationship with hospital carers “...If you have a particular doctor that you see all the time the doctor will get to know if you’re pretending or if it’s real...” (focus group 3.2) If nursing staff had received training in SCD “As for nurses on sickle cell ward, they know you so in a way you’re used to them so it doesn’t mean they’re friendlier to you but you can get on with them....Only when you go to outside the sickle cell ward that you tend to have a problem” (focus group 4.1). A health care professional (also an SCD patient) felt she was treated well by hospital staff “It has come to light over the years that I’m a medical person as well, so they know how to relate to me, and they know I’m only there because I’ve got the pain and once the pain is over I’m going away” (focus group 3.2). High turnover of junior staff and unavailability of consultants reduced the patients experience of positive treatment in hospital “A consultant isn’t the person you’re dealing with on a day to day basis anyway. They’re the ones you see infrequently so they’re not as important, it’s the junior doctors you have to see every day, or the nurses” (focus group 4.1) Mistrust, Neglect Control and stigmatisation: (NB- these themes are as identified in Maxwell et al [1999]). In addition patients reported that mistrust motivates many health care professionals to exert control over patients which has significant implications for pain management. Family members may be involved without the patients’ consent “You’re twenty-five and you’re making decisions for yourself and the trouble with doctors is with sickle patients they have the nerve if you make a decision and they don’t like it, to go and still talk to your parents when you’re supposed to be making a decision for yourself” (focus group 2.1) Mutual mistrust and alienation: Many patients with SCD felt alienated because of the control exerted by healthcare professionals. They started to mistrust their healthcare professionals which had implications on pain management. “As far as the doctors are concerned they already think you are in here just for the injections, if they see ‘refused’ by an oral painkiller, that just gives them more ammunition, so whether I throw that tablet out the window, or whatever, (I tell the nurses) ‘Do not put ‘R’ on my chart’” (Interview 8.1). Patients may not want to discuss concerns about medication use (dependence, tolerance and withdrawal symptoms) because they believe they may be stigmatised as a drug addict. This can also lead patients to avoid discussing non-medical aspects of their pain or pain management (such as emotional issues or stress) because they worry that pain will be explained away. “They only treat you for one thing when you go into hospital, you need to be treated for your stress as well, you need to talk about what’s bothering you but that is not an issue. I went into a state where I was practically suicidal and nobody recognised nothing except I had sickle cell crisis...”(focus group 1.2). Support:

	The study identified that people living with sickle cell disease need various kinds of support from different sources. All participants reported that a lack of support for people living with sickle cell disorders contributed to frequency of hospital admissions. Patients managing pain at home felt vulnerable to isolation in that most support services were hospital based and patient support groups were perceived to be ineffective or irrelevant. Patients reported issues such as a lack of progress made in such groups, and having little in common with other group members. Many participants were also unaware of the support services available via haemoglobinopathy centres. Three main types of support were identified: Psycho-social support: Participants recognised the need for training in cognitive pain management techniques, distraction methods, and having someone understanding to talk to. Clinical support: Participants required information about medication use, including side effects and dispensation of medication and oxygen at home Support after discharge from hospital: Participants reported that this time was difficult due to issues such as: Physical weakness, making it difficult to undertake basic tasks Withdrawal symptoms after coming off strong medication Isolation and loneliness Difficulties with psychological readjustment. "I had withdrawal symptoms... the first time it ever happened to me it was horrible. I had my son holding me down, I was getting cold turkey, stomach ache, diarrhoea, vomiting and the bed is shaking and you don't know what the hell is happening to you 'cause nobody's ever told you that this drug can do this to you, so it's like, really scary" (focus group 2.1). Most participants reported a lack of care and support after discharge. This may have an influence on readmission rates and overall time spent in hospital. Readmission shortly after discharge was common. It may be a cyclical issue of repeat readmissions due to lack of support once discharged.
Source of funding	Kings Fund Report produced by financial support from Roald Dahl Foundation & St James' Trust
Limitations	Full and clear reporting of theoretical approach, data collection, validity of qualitative methodology and data analysis. NB: This also provides resolutions to questions about the quality appraisal for Maxwell et al (1999)
Comment	Single centre study only Study appeared to focus upon pethidine as the main method of pain management UK Study

Table 84 Evidence table for Harris et al (1998)

Study ID	Harris et al (1998) Ref ID: 6438
Aim	To examine sickle cell (SC) patients experiences of living and coping with the disease To examine SC patients experiences of haemoglobinopathy ward and related services

	To assess SC patients levels of psychological distress
Theoretical approach	Not described
Data collection	A mixed design was used including both a qualitative interview and quantitative questionnaire. The interview lasted for approximately 2 hours and followed a standardised sequence of questions (both qualitative and quantitative). The interview incorporated demographic info, general comments on hospital service, patients' history of disease over the last year, circumstances surrounding admission, subsequent experience of hospital service, use of analgesia, pain coping techniques, impact of SCD on patient's life, psychological or emotional support received in hospital. Patients also completed the SCL (Symptom Checklist-90) questionnaire to provide an overall measure of psychological distress Some participants were interviewed at home while others were interviewed in the hospital at the end of their stay
Method & process of analysis	The specific methods used to collate and analyse the qualitative data were not reported. Nine subscales on the SCL 90 were aggregated to provide a GSI (Global Severity Index) an overall measure of psychological distress.
Population & sample collection	All participants had been previous in-patients at the hospital. Only participants that had been admitted within the last 12 months were eligible for inclusion. 30 consecutive adult in-patients who were admitted (within the last year) to a London hospital for a vaso occlusive episode were approached. 27 patients agreed to take part. 15 males (mean age 28 years, range 21-35), 12 females (mean age 30 years, range 18-60) and all participants were Afro-Caribbean
Key themes	The following themes were identified: <u>Experience of last admission:</u> Decision to come into hospital: Two thirds of patients (67%) would only come into hospital when pain was too much to handle at home. Many patients had struggled to cope with pain at home for a number of days before coming to hospital and only when pain was unbearable would they come into hospital. <u>Waiting for analgesia:</u> More than half of the patients (56%) had received analgesia within 15 min of their arrival in A&E. More than one third of patients (36%) were not given an explanation for the delay. <u>Opportunities to discuss problems</u>: Over half of the patients interviewed (59%) were satisfied that they had had the opportunity to discuss concerns with a healthcare professional but some would like the opportunity for further contact with Drs, SC Counsellor, psychologist, or social worker. Although 85% would have been interested in discussing their concerns further with a member of staff. A list of appropriate professionals that the patients would prefer to talk to included doctor (n=18) sickle cell counsellor (n=18), psychologist (n=12), social worker (n=12), nurse (n=8), priest or other religious person (n=2). <u>Pain control:</u> For the majority of patients (56%) pain took three or more days to reduce to tolerable levels. Most patients were offered intramuscular injections. One third were offered non-steroidal analgesics. Overall patients were satisfied with pain control but some patients suggested pain control would improve if they did not have to ask for analgesics to be given. <u>Pain coping methods</u>: These had varying degrees of helpfulness – 96% of patients stayed in bed to cope with pain but only 88% found it helpful. Other methods included analgesic medication, rocking , positive thinking, distraction, rubbing affected part and listening to music. There was much less reliance on cognitive behavioural techniques but over one third used relaxation exercises but only 33% found it useful Withdrawal from medication and dependency Most patients (63%) experienced some withdrawal difficulties and worried about becoming dependent on analgesia

	Experience of hospital services 63% stated that hospital services were satisfactory to good. 44% cited negative attitudes of staff towards people with SCD as a criticism. These included complaints that staff were biased against people with SCD, and were afraid to come to the hospital because of the attitudes of the nurses. Over a quarter of patients (26%) also thought staff generally had poor knowledge or understanding of SCD. "... but when you feel pain you expect to have some immediate reaction to the situation and you might not be as calm as expected. A lot of doctors and nurses are offended and not sympathetic. They don't realize that by the time we arrive at the hospital we're in a lot of pain". Some patients (22%) thought that the staff did not appreciate the patients were in pain and treated them as 'liars'. Five patients thought nurses were slow to provide analgesia. "Sometimes if they don't understand what triggers [the pain] then they think that you're lying" "We should get pain relief immediately instead of them taking care of the pillows" "They're very slow to get painkillers, they don't appreciate the pain you're in" Psychological symptoms Results from the SCL 90R identified that most patients were experiencing psychological distress One quarter were in the severe range
Source of funding	Not reported
Limitations	Not sure how rigorous or defensible the design was - Rationale behind the choice of standardised interview was not provided Inadequate reporting of data collection and interview process to determine how well data collection was carried out No justification for not triangulating methods – the study only used a standardised interview Considerations of context bias were not explored (i.e., the settings for the interview varied between hospital and at home) The data findings could have been more thorough- summarised only, cross referencing and discrepancies were not explored in detail Ethical considerations were not reported
Comment	UK study – London setting Adults only

Table 85 Evidence table for Mitchell et al (2007)

Study ID	Mitchell et al (2007) Ref ID: 646
Aim	To assess how health care delivery can be optimised to improve patient and family coping and service utilization.
Theoretical approach	Not reported

Data collection	Mixed design using both qualitative (focus group) and quantitative (questionnaire) design The Coping Strategies questionnaire included force choice response across a 6-point Likert scale. The CSQ was used to provide an overall measure of how often participants use cognitive, behavioural and physiologic coping strategies. The Family Assessment Device was a 60-item questionnaire to measure family functioning across 7 dimensions using a 4-point Likert scale. Participants were invited by letter to take part and all participants were called to meet one week later. Participants took part in an initial 30 min social event whereby they completed the questionnaire. Then participants were then assigned to focus group discussions. Eight focus groups took place across three large urban children's hospitals. Discuss ions with parents lasted 60 to 75 minutes, discussions with children lasted 45to 60 minutes Each focus group was facilitated through open ended questions. Questions were developed through meetings with site collaborators and organised around the primary goals of the study. The open-ended questions were drafted and refined in several meetings across all sites, with experts of SCD management and interventions, SCD and chronic illness research and experts in focus group / qualitative analysis. Questions covered perspectives of pain management and care and family and patient coping. Eight focus groups were conducted by a trained moderator. Participants took part in 1 of 8 groups All focus groups were conducted by a trained moderator using a standardised format and followed a standard introduction describing the purpose of the group and general conduct. Acceptable prompts were identified a priori and used for each question as a means to standardise conduct of the groups across the three sites. The moderator summarised points that were raised after each discussion and participants were allowed to augment their responses as needed.
Method & process of analysis	Data from each phase (parent and patient information) was analysed and summarised separately by three trained coders using consensus ratings. Each transcript was assigned so that it had at least one coder from the transcript site, one off-site coder and one independent coder who was not involved in the focus groups. Coders summarised the data and independently coded the transcripts based upon the following criteria: Question/prompt, major themes, minor themes, other topics/discussions. Transcripts were then assessed for within group/ across site consensus using a 2-step process, comprising consensus of major themes for which all coders agreed within group and cross site consensus. The report focused upon cross-site consensus themes.
Population & sample collection	Participants were recruited via letters, telephone calls and clinic visits. Eligibility criteria for parents included the following: They had to be living with the child and had to have been the primary caregiver for at least 12 months prior to the study commencement. Parents of children with well-documented developmental delays or documented severe neurologic brain damage were not contacted for participation. Participants arriving after the first 15 minutes of the group were also excluded (this was to preserve integrity of group dynamics across each site) Fifty three parents/ guardians representing 48 children with SCD were recruited (the sampling method used was not reported) 46 female (43 mothers/ foster mother, 3 grandparent/ aunt) 6 male (3 fathers 3 uncles/ caregiver) Mean age of child being represented was 10.7 years, (children = 50% male, 50% female)
Key themes	<u>Parent and family coping highlights</u> Parents rely on their children to monitor symptoms, and tell them when they are experiencing pain. Parents also acknowledged that children will provide cues to help parents make decisions regarding treatment recommendations. This can be with children aged as young as 5. Parents reported that their

	ability to make independent decisions without child input is therefore limited. "When he [grandson] was about 5, I started relying more on what he was telling me versus what I was seeing" <u>Parent recommendations for improving care</u> Parents expressed a need for increased support, education and sensitivity to parent/ carers from healthcare workers Parents would like to see more increased staff training and provision of more medication dispensing/options and were frustrated at staff being poorly trained. "I knew we were in trouble when the nurse looked at me and said 'so... how long has your daughter had sickle cell disease?' She didn't even know it was an inherited condition" They highlighted the importance of providing more community education for SC patients/ carers to develop awareness. Parents were also frustrated with the limited attention SCD relatives received in comparison to other chronic paediatric illnesses. <u>Issues identified from the questionnaire- Patient and family coping and health care utilization</u> There was a relationship between patient and family coping and coping strategies. Patients with less adaptive coping skills have families that function less adaptively. Children with less adaptive coping strategies have a greater use of the ED. Children are agents in their own healthcare and disease management and educational approaches could include children
Source of funding	Not reported
Limitations	Data analysis could have had more depth- although participant excerpts were provided the appraisal of these findings could have been more detailed Although confidentiality was considered it is not reported whether the study was approved by an ethics board
Comment	US study based at 3 large urban children hospitals Paediatric population

Table 86 Evidence table for Waters & Thomas (1995)

Study ID	Waters & Thomas (1995) Ref ID: 2100
Aim	To identify the perceptions and expectations of pain management of patients with SCD and of nurses
Theoretical approach	Not reported
Data collection	A qualitative questionnaire was used (unsure if open ended/ or forced choice or structured/ semi structured etc.). Participants completed the questionnaire in the presence of the researcher. A forced choice structured questionnaire provided to nurses. Validity and reliability of the questionnaire was not reported.
Method & process of analysis.	Both quantitative and qualitative analysis performed Demographic data was collated and quantitative analysis was performed to identify the amount of time spent in hospital, sick days etc. Key themes from the questionnaire were identified and explored using qualitative assessment, although the specific method of

	identifying themes was not reported.
Population & sample collection	Data was collected from 9 patients (6male 3 female, age 17-28, mean age 24.3) who were admitted to a general medical ward for SCD. Data was also collected from 12 qualified nurses plus 5 student nurses on the haematology ward. The chosen sampling method to identify the target population was not reported.
Key themes	Demographic data During the 12 months before investigation: The average participant length of stay was 12.7 days The average time spent in hospital was 33.3 days (range 0-90 days) The average knowledge score for patients about SCD was 5.3/10 The average knowledge score of nurses about SCD was 1.8/10 Pain experience: Nurses aimed to achieve full pain relief, but this was not supported by patients' experiences. Only 4 patients experienced complete pain relief at any one point; 3 patients experienced continuous pain; 5 patients experienced remittent pain and1 patient experienced intermittent pain. Unsatisfactory pain management was shown in comments such as: "I wish they [the nurses] could deal with you when they say they will instead of forgetting" and "They [the nurses] don't have to say anything but you can just tell sometimes that they don't agree with having to give you an injection". Six nurses mis-located the site of their patients' pain. Two thirds incorrectly estimated the severity of the patients' pain and seven nurses incorrectly estimated the duration of pain. Seven patients felt less in-control of pain while in hospital (compared to home). Seven patients reported they wanted to be more involved in the management of their own pain while on the ward Five patients perceived nurses sympathy to be average (3/5) Pain assessment: Assessment of pain was unplanned and sporadic although nurses reported they usually assessed pain on a continual basis. All patients reported they had to ask for more analgesia when needed Factors hindering effective pain relief: Thirteen nurses felt sickle cell pain could be best relieved with analgesia, but they reported that factors such as time (n=4), lack of knowledge about narcotic analgesia (n=4) and worries about patient overdosing, n=4) and their lack of experience with SCD patients (n=2) limited their ability to provide adequate relief. Twelve nurses said they could provide better pain relief using 'alternative' methods, but they reported their ability was limited by time (n=6), lack of knowledge about the methods (n=7), and lack of experience (n=9). Five nurses reported they could not provide better pain relief in SC patients by using methods such as heat treatment. Four patients reported nurses rarely provided complementary alternatives verbal support or comfort measures and five patients reported this never happened. Five patients would have liked more health care advice and information about self-care and pain relieving measures. Eight patients would have liked more emotional support from nurses.
Source of funding	Not reported
Limitations	Questionnaires were completed in the presence of a researcher- but the role of the researcher has not been clearly reported- a lack of reflexivity could influence the validity

	Context bias has not been adequately considered in the reporting the settings Unclear about sampling strategy- how potential participants were identified Lack of clear reporting of distribution and assessment of questionnaire Methods used for data analysis were not reported Ethical issues were not reported
Comment	UK Study Adult population

Table 87 Evidence table for Lattimer et al (2010)

Study ID	Lattimer et al (2010). Ref ID:
Aim	To measure the in-hospital experience of patients who received care during vaso –occlusive crises and compare the experiences to a national sample of hospitalised patients
Theoretical approach	Not reported
Data collection	Interviews were conducted with 45 patients admitted to hospital, Participants were drawn from a large cohort of patients with SCD at an urban medical centre. Participants were interviewed shortly before discharge (within 24 hours of discharge or at least within 5 days of discharge) to assess their hospital experiences Measures comprised the Picker Patient Experience questionnaire (PPE-15) which coded items dichotomously to indicate the presence or absence of a problem. The PPE was an established validated tool for measuring patients' hospital experiences.
Method & process of analysis	Analysis was limited to the sub-set of patients that were admitted and in the case of multiple admissions only data from the first admission was used. Descriptive statistics were used to describe study sample. Percentage scores from participants identifying a problem PPE were compared with national average scores. Correlates of the number of reported problems were also examined. Interviewing was conducted in person (if the interview was conducted within 24 hours of the patients discharge or via the phone if the interview was conducted within a few days of discharge. The relationship of the researcher with the participants was not reported.
Population & sample collection	Forty five eligible patients were recruited from the adult sickle cell and haematology outpatient clinics and the emergency department, mean age = 31.2 (range 20-59, 25 female, 20 male). Each time a participant from this cohort was admitted for a VOC they were interviewed (although specific sampling methods were not reported).
Key themes	<u>Problematic patient hospital experiences</u>: Patients thought:

	They were insufficiently involved in decisions about their own medical care (86%). Staff gave conflicting information (64%) It wasn't easy to find someone to discuss concerns (61%) Doctors answers to questions were not always clear (58%) nurses answers to questions were not always clear (56%) Doctors did not always discuss patients' fears or anxieties (53%) and nurses did not always discuss patients' fears or anxieties (52%) Patients were not always treated with respect or dignity (50%) Staff did not do enough to control pain (50%) Families were not given enough information to help with recovery (37%) Families didn't get the opportunity to talk to a doctor (36%) Doctors sometimes talked as though patient wasn't there (36%)
Source of funding	Not reported
Limitations	Interviews were conducted by a researcher but their role has not been clearly reported Context bias has not been adequately considered in the reporting of the interview settings
Comment	USA Adult population

Table 88 Evidence table for Murray & May (1988)

Study ID	Murray & May (1988) Ref ID: 2620
Aim	To collect information from patients' on various aspects of pain crises both in hospital and at home
Theoretical approach	Not reported
Data collection	A structured questionnaire was used to obtain information on patients' awareness of sickling crises, the measures they take to avert or control a crisis, and previous sources of health education, accessibility and adequacy of medical care, including perception of factors causing crises. The questionnaire included forced choice and open ended comments A linear analogue scale (0-5) was used to obtain patient info about pain intensity, perceptions of healthcare professionals understanding and problems of SCD. A linear analogue scale (0-3) was used to obtain information about patients' perception of pain. Other questions were forced choice (with space for additional comments) Details about the validity and reliability of the questionnaire were not reported.
Method & process of analysis	Four hundred questionnaires were distributed to haematology clinics in London, Manchester and Birmingham, UK, to be completed by Sickle cell patients attending the clinics.

	The method of administration and distribution was not specifically reported. Data was collected for all subgroups. Genotypes of sickle cell patients included HbSS, HbC, Hb and H-β thalassaemia The Mann-Whitney test showed no significant difference of results between groups and therefore results were combined and quantified
Population & sample collection	102 patients (61 female (41 male, aged 11-49 years) completed the questionnaire from the original 400 questionnaires that were distributed to the three clinics. The response rate is unknown because number of questionnaires given to patients is unknown. Participant eligibility and details of exclusions were not described. All participants were patients attending sickle cell and haematology clinics in London, Birmingham and Manchester 77 homozygous HbSS 21 heterozygous HbSC 1 heterozygous HbSJ, 1 H-β thalassaemia The remainder did not know their genotype
Key themes	<u>Patient experiences during prodromal stage:</u> Personal management of pain was similar before and during periods of pain. Self-treatment methods included keeping warm, taking extra fluids, getting rest and taking painkillers. Other measures used included relaxation (used more in period before pain rather than during), taking extra vitamins, herbal remedies and talking about fears (practised less frequently during crises rather than before). Eighty one respondents had received some information and advice about the self-management of sickle cell disease. The hospital doctor was the main source of information (n=45), most respondents thought the information they received was comprehensive (n=79) and believed that it had helped them (n=70). <u>Experiences of pain management at hospital:</u> Patients felt that staff in the A&E department were the least able to understand problems associated with SCD. Eighty eight patients sought professional help at the hospital. Some thought they were seen quickly (n=18) and some thought the delay in being seen was too long 9n=33). Some patients reported receiving analgesics on demand (n=23), and some thought pain relief was available when needed (n=40) but 40 respondents did not think pain relief was available when needed. Most patients had worries about the drug they were given. These included concerns about side effects (n=17), overdosing (n=1) and addiction (n=6). Some participants thought pain relief was available when needed (n=40), some patients thought it was not always available (n=29).
Source of funding	Not clear but credit given to Blood Research Fund and Sickle Cell Society for assistance with research
Limitations	Method of administration and distribution is unknown Context bias has not been adequately considered in the reporting the settings Unclear about sampling strategy- how potential participants were identified Unclear if an existing tool or new tool was developed: The tool has not been described in any detail (i.e., development, testing and piloting of questionnaire has not been reported). Ethical considerations were not reported
Comment	UK study

	Multi-centre study based in 3 UK hospitals (London, Birmingham and Manchester) Includes both adults and children

GRADE profiles

Review Question 1: Pharmacological management

Table 89 GRADE profile for primary analgesia

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
Pain rating at 4 hours (assessed with: Visual Analogue Scale [VAS]) in adults											
NSAID [IM ketorolac] vs. placebo [IM saline]											
1 (Wright et al 1992)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	none	12 visits (total 18 patients)	12 visits	Overall mean change from baseline was -2.63 in ketorolac group and -4.23 in the placebo group Mean difference (MD) = 0.70 (95% CI -1.90 to 3.30)	Moderate	Critical
Pain rating at 8 hours (assessed with: Visual Analogue Scale [VAS]) in adults											
PCA morphine vs. intermittent IV injection											
1 (Gonzalez et al 1991)	randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	none	15 cases in 10 patients PHASE 1	15 cases in 10 patients PHASE 1	Mean change 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,	Low	Critical
							17 cases in 13 patients PHASE 2	23 cases in 12 patients			

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
								PHASE 2	1.29)		
Pain rating 2 days after treatment (assessed with: 11 point verbal response scale, 0-10, with 0 indicating no pain) in adults											
PCA morphine vs. IV morphine											
Van Beers et al 2007	randomised trial	No serious risk of bias	No serious inconsistency	No Serious indirectness	Serious[a]	None	25 episodes in 19 patients		Mean verbal response pain score did not significantly differ in the PCA group (5.3, CI 4.5-6.9) compared to 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											
NSAID [IV ketoprofen] vs. placebo [saline]											
1 (Bartolucci et al 2009)	randomised trial	No serious risk of bias	No serious inconsistency	No Serious indirectness	Serious[a]	None	26	26	Median change from baseline was -6.04 in the ketoprofen group and -6.14 in the placebo group. Median VAS score in Ketoprofen (1.26, IQR 0.48 to 2.32) and placebo (0.96, IQR 0.58 to 3.32) did not significantly differ (p = 0.5)	Moderate	Critical
NSAID [IV ketorolac] vs. placebo [IV saline]											
1(Perlin et al 1994)	randomised trial	No serious risk of bias	No serious inconsistency	No Serious indirectness	Serious[a]	None	9	11	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, -	Moderate	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									0.28)		
									MD (day 5) = -2.08 (CI -4.28, 0.12)		
PCA morphine vs. IV morphine											
1 (Van Beers et al 2007)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	25 episodes in 19 patients		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 and did not significantly differ (p = 1.00)	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											
NSAID [IV ketoprofen] vs. placebo [saline]											
1 (Bartolucci et al 2009)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	26	26	Median CPS did not significantly differ between the ketoprofen (0.4, IQR 0.2 to 0.7) and placebo groups (0.4, IQR 0.2 to 0.7, p = 0.46)	Moderate	Critical
NSAID [IV ketorolac] vs. placebo [IV saline]											
1 (Perlin et al 1994)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	9	11	Mean VPS was significantly lower in the ketorolac (1.1) compared to 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											
NSAID [IV ketorolac] vs. placebo [IV saline]											
1 (Perlin et al 1994)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	9	11	Mean pain relief score did not significantly differ in the ketorolac (2.7) and placebo groups (2.4, p > 0.05)	Moderate	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
Amount of analgesia used in adults											
NSAID [IM ketorolac] vs. placebo [IM saline]											
1 (Wright et al 1992)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	12 patient visits	12 patient visits	At 4 hours the mean amount of meperidine used in the ketorolac group (231 mg, SD 92) did not significantly differ compared to the placebo group (250 mg, SD 85, p = 0.61)	Moderate	Critical
NSAID [IV ketorolac] vs. placebo [IV saline]											
1 (Perlin et al 1994)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	9	11	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
NSAID [IV ketoprofen] vs. placebo [saline]											
1 (Bartolucci et al	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	26	26	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
PCA morphine vs. intermittent IV injection											

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
1 (Gonzalez et al 1991)	randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[a]	None	15 cases in 10 patients PHASE 1	15 cases in 10 patients PHASE 1	PHASE 1 The total number of doses was significantly higher in the PCA group (35.5 ± 23.5 mg) compared to the IV group (6.5 ± 2.6 mg, p = 0.0006). However, the total amount of morphine administered did not significantly differ between the PCA (35.5 ± 23.5 mg) compared to the IV group (28.8 ± 13 mg, p = 0.269)	Low	Critical
							17 cases in 13 patients PHASE 2	23 cases in 12 patients PHASE 2	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 significantly differ between IV and PCA groups (41.0 ± 17.6 vs. 34.6 ± 20.9 mg, p = 0.945)		
PCA morphine vs. IV morphine											
1 (Van Beers et al 2007)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	25 episodes in 19 patients		The median morphine dose was significantly lower in the PCA group (0.5 mg/hr, IQR 0.3-0.6) compared to the IV group (2.4 mg/hr, IQR 1.4-4.2, p = 0.001). The median total morphine dose was also significantly lower in the PCA group compared to the IV group (33, IQR 10-68 vs. 260mg, IQR 204-529, p = 0.02)	Moderate	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
Use of additional/rescue doses of analgesia in adults											
PCA morphine vs. intermittent IV injection											
1 (Gonzalez et al 1991)	randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	15 cases PHASE 1 17 cases PHASE 2	15 cases PHASE 1 23 cases PHASE 2	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
PCA morphine vs. IV morphine											
1 (Van Beers et al 2007)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	6/12	5/13	RR 1.30 (CI 0.53, 3.17) for requiring an increased dose if there is no adequate pain relief	Moderate	Critical
Duration of the painful episode in adults											
NSAID [IV ketoprofen] vs. placebo [saline]											
1 (Bartolucci et al 2009)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	26	26	Median duration of VOC did not significantly differ in the ketoprofen group (51 hours, IQR 35.5-87) compared to the placebo group (50 hours, IQR 36-103)	Moderate	Important
Adverse events in adults											
Ketorolac vs. placebo											
1 (Wright et al 1992)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	0/12 visits	0/12 visits	No side effects were reported in either group	Moderate	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
NSAID [IV ketoprofen] vs. placebo [saline]											
1 (Bartolucci et al 2009)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	16 events in 33 patients	19 events in 33 patients	The types and frequencies of adverse events were similar for the two groups (events include nausea, vomiting, pruritus, constipation and epigastralgia)	Moderate	Critical
PCA morphine vs. intermittent IV injection											
1 (Gonzalez et al 1991)	randomised trial	Serious[b]	No serious inconsistency	No serious indirectness	Serious[c]	None	PHASE 1 7/15 PHASE 2 9/17	PHASE 1 8/15 PHASE 2 15/23	PHASE 1: RR 0.88 (CI 0.43, 1.80) PHASE 2: RR 0.81 (CI 0.47, 1.39) these included nausea and vomiting, pruritus and difficulty to arouse	Low	Critical
PCA morphine vs. IV morphine											
1 (Van Beers et al 2007)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	12 episodes	13 episodes	The AUC 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 infusion group. No significant differences were found for pruritus and sedation.	Moderate	Critical
LOS in adults											
NSAID [IV ketorolac] vs. placebo [IV saline]											

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
1 (Perlin et al 1994)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	9	11	The median duration of hospitalisation was significantly lower in the ketorolac group compared to the placebo group (3.3. vs. 7.2 days, p < 0.05)	Moderate	Critical
PCA morphine vs. intermittent IV injection											
1 (Gonzalez et al 1991)	randomised trial	Serious[b]	No serious inconsistency	Serious[e]	Serious[a]	None	15 cases in 10 patients PHASE 1	15 cases in 10 patients PHASE 1	PHASE 1: MD = 0.60 hours (CI -1.65, 2.85)	Very low	Critical
							17 cases in 13 patients PHASE 2	23 cases in 12 patients PHASE 2	PHASE 2: MD = 0.20 hours (CI -0.92, 1.32)		
PCA morphine vs. IV morphine											
1 (Van Beers et al 2007)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	12 episodes	13 episodes	There were no significant differences in the median admission duration in the PCA group (6.0 days, IQR 4.3-9.3) compared to the IV group (9.0 days, IQR 6.0-12.0, p = 0.15)	Moderate	Critical
Pain rating at 2 hours (assessed with: Visual Analogue Scale [VAS] 0-10, with 0 indicating no pain) in children											
NSAID [ketorolac] vs. opioid [pethidine]											
1 (Grisham & Vichinsky 1996)	randomised trial (cross over trial)	Serious[d]	No serious inconsistency	No serious indirectness	Serious[a]	none	20	20	Patients receiving ketorolac had significantly larger decreases in VAS scores over 150 minutes compared to the meperidine group (p < 0.001). The greatest decrease in pain scores	Low	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
									occurred in first 30 minutes for both drugs (ketorolac = 3.9, meperidine = 5.4, p < 0.001)		
1 (Grisham & Vichinsky 1996)	randomised trial (cross over trial)	Serious[d]	No serious inconsistency	No serious indirectness	Serious[a]	none	20	20	There was no significant difference in VAS scores of either group (meperidine then ketorolac or ketorolac then meperidine) after 150 minutes (mean VAS ketorolac/mepidine = 3.8, meperidine/ketorolac = 5.1)	Low	Critical
Pain rating at 6 hours (assessed with: Visual Analogue Scale [VAS]) in children											
(NSAID [IV ketorolac] vs. placebo [IV saline])											
1(Hardwick et al 1999)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	22 visits	19 visits	Overall mean change from baseline was -2.26 in ketorolac group and -0.42 in the placebo group MD (1h) = -0.09 (CI -1.71, 1.53) MD (2h) = -0.59 (CI -2.25, 1.07) MD (3h) = -1.06 (CI -3.17, 1.05) MD (4h) = -1.20 (CI -2.95, 0.55) MD (5h) = -1.41 (CI -3.07, 0.25) MD (6h) = 0.70 (CI -1.90 to 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											
NSAID [IV ketorolac] vs. placebo [IV saline]											
Adawy et al (2005)	randomised trial (3 arms)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	15	15	Median NFPS scores were significantly lower in the ketorolac group (2, range 1-2) compared to the placebo group	Moderate	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
									(3, range 2-3, p < 0.05)		
Corticosteroid [IV methylprednisolone] vs. placebo [IV saline]											
Adawy et al (2005)	randomised trial (3 arms)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	15	15	Median NFPS scores were significantly lower in the methylprednisolone group (2, range 1-2) compared to the placebo group (3, range 2-3, p < 0.05)	Moderate	Critical
Pain rating (assessed with various scales: OUCHER on a 0-100 scale, CHEOPS, Faces and clinical assessment) in children											
Oral morphine vs. IV morphine											
1 (Jacobson et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	24	26	The mean differences between the oral group and the IV group were not significantly different for any of the pain assessments (p > 0.05)	Moderate	Critical
Amount of analgesia used in children											
NSAID [IV ketorolac] vs. placebo [IV saline]											
2 (Hardwick et al 1999, Adawy et al 2005)	randomised trial	Serious[f]	No serious inconsistency	Serious[g]	Serious[a]	None	37	34	Pooled MD = -0.01 mg/kg/hr (95% CI -0.03, 0.00), p = 0.07 (see forest plot).	Very low	Critical
Oral morphine vs. IV morphine											
1 (Jacobson et al 1998)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	24	26	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

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
Use of additional/rescue doses of analgesia in children											
NSAID [IV ketorolac] vs. placebo [IV saline]											
1 (Adawy et al 2005)	randomised trial (3 arms)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	15	15	MD (mean rescue doses) = -1.10 mg (CI -1.84, -0.36)	Moderate	Critical
Oral morphine vs. IV morphine											
1 (Jacobson et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[a]	None	24	26	MD (mean rescue doses/day) = -0.20 (CI -0.62, 0.22)	Moderate	Critical
Adverse events in children											
NSAID [IV ketorolac] vs. placebo [IV saline]											
1 (Hardwick et al 1999)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	22 visits in 13 patients	19 visits in 9 patients	One patient experienced local histamine reaction to morphine and no other adverse events were noted	Moderate	Critical
1 (Adawy et al 2005)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	15	15	There were significantly fewer events of nausea (2 vs. 9) and vomiting (1 vs. 7, $p < 0.05$) in the ketorolac group compared to the placebo group. There were no significant differences in the number of pruritus events (2 vs. 2).	Moderate	Critical
Oral morphine vs. IV morphine											
1 (Jacobson et al 1997)	randomised trial	No serious risk of	No serious inconsistency	No serious indirectness	Serious[c]	None	27	29	The frequency and severity of adverse events did not differ significantly between the two	Moderate	Critical

Quality assessment							No of patients		Effect/outcome	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
		bias							groups (62 vs. 52 reports, 16 vs. 19 severe intensity events). Common events included fever, pruritus, nausea and vomiting and constipation		
Readmission within 48 hours in children											
NSAID [IV ketorolac] vs. placebo [IV saline]											
1 (Hardwick et al 1999)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	3/13	0/9	RR 5.00 (CI 0.29, 86.43)	Moderate	Important
1 (Adawy et al 2005)	randomised trial (3 arms)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	0/15	0/15	No patients returned to ED within 48 hours	Moderate	Important

‡ adapted from McGill-Melzack scale
[a] Downgrade by one level: for continuous variables the imprecision criteria was downgraded if the 95% CI crosses the MID (the GDG agreed that this is 3 for pain ratings using a VAS scale and 2 days for length of stay) or if the total sample size is less than 400 (rule of thumb from GRADE)
[b] Downgrade by one level: unclear method of randomisation and some patients completed both phases
[c] Downgrade by one level: for binary variables the imprecision criteria 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)
[d] Downgrade by one level: wash out period 2.5 hours
[e] Downgrade by one level: LOS in the emergency department
[f] Downgrade by one level: in one study additional doses of morphine was given 2 hourly based on VAS
[g] Downgrade by one level: morphine delivered by different routes (PCA and IV)

Table 90 GRADE profile for pharmacological management of the underlying sickling process

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
Pain rating at 4 hours (assessed with: Visual Analogue Scale [VAS]) in ADULTS											
Nitric oxide vs. placebo											
1 (Head et al 2010)	randomised trial	Serious[a,b]	No serious inconsistency	No serious indirectness	Serious[c]	none	9	9	The mean total reduction was 6.3 (SD 2.2) in the nitric oxide group vs. 2.97 (SD 2.1) in the placebo group (p = 0.02)	Very low	Critical
Pain rating up to 24 hours (assessed with: Visual Analogue Scale [VAS], 0-10, with 0 indicating no pain) in adults											
Nitric oxide vs. placebo											
1 (Gladwin et al 2011)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	75	75	Baseline VAS 7.7 in nitric oxide group and 7.6 in placebo MD (mean VAS at 24h) = 0.10cm (95% CI -0.86 to 1.06)	Low	Critical
Vasodilator [isoxsuprine] vs. opioid [pethidine]											
1(Al-Jama et al 1999)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	23 episodes (total 43 patients)	21 episodes (total 43 patients)	Mean change from baseline -5 in both isoxsuprine and meperidine groups (from 10 at baseline in both groups) MD* (30mins) = 2.00 (CI 0.82, 3.18) MD (1h) = 1.60 (CI 0.25, 2.95) MD (2h) = 0.70 (CI -0.89,	Low	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									2.29)		
									MD (6h) = 1.00 (CI -0.77, 2.77)		
									MD (24h) = 0.00 (SE 0.91, 95% CI -1.77 to 1.77)		
Pain rating at 7 days (assessed with: Visual Analogue Scale [VAS]) in adults											
Non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Orringer et al 2001)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	126	123	Mean difference (MD) = 8.70 U/h (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											
Non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Adam-Graves et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d,g]	Serious[c]	None	18	13	Median pain intensity ratings did not significantly differ between PP188 (median = 0.8) and placebo group (median = 1.4, p=0.07†)	Very low	Critical
Amount of analgesia used in adults											
Non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Adam-Graves et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d,g]	Serious[c]	None	18	13	The use of parenteral analgesics did not significantly differ in the PP188 group compared with the placebo group (median 47 vs. 149 mg, p = 0.02) when an	Very low	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									intention to treat analysis was adjusted for baseline pain		
2 (Orringer et al 2003, Adam-Graves et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d,g]	Serious[c]	None	126	123	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
Nitric oxide vs. placebo											
1 (Gladwin et al 2011)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	75	75	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 to the placebo group (0.23, IQR 0.07-0.70, p = 0.74). There was also no difference in the total median opioid use between the groups (2.8, 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											
Non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Adam-Graves et	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d,g]	Serious[c]	None	18	13	The median duration of painful episodes did not	Very low	Important

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
al 1997)									significantly differ between the PP188 group (67, range 12-178) and the placebo group (80 hours, range 12-315, p = 0.182)		
1 (Orringer et al 2001)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	126	123	MD = -4.81 hours (CI -15.03, 5.41)	Low	Important
Vasodilator [isoxsuprine] vs. opioid [pethidine]											
1 (Al-Jama et al 1999)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	23	21	The median duration of the painful episode did not significantly differ between the isoxsuprine group (24 hours, range 8-120) compared to the opioid group (48 hours, range 24-168, p =0.44)	Low	Important
LMWH [tinzaparin] vs. placebo [saline]											
Qari et al (2007)	randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	127	126	MD = -1.78 days (CI -1.94, -1.62)	Low	Important
Nitric oxide vs. placebo											
1 (Gladwin et al 2011)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	75	75	Median time to VOC resolution did not differ significantly in the nitric oxide group (73 hours, CI 46.0-91.0) compared to the placebo group (65.5 hours, CI 48.1-84.0, p = 0.87)	Low	Important

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
Adverse events in adults											
non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Adam-Graves et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d,g]	Serious[e]	None	28	22	Adverse events were similar in the PP188 group (28) and the placebo group (16), most of these were mild or moderate in intensity. One serious adverse event (transient increase in serum creatinin) was attributable to the study medication	Very low	Critical
1 (Orringer et al 2002)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[e]	None	126	123	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 one death in the PP188 group due to pulmonary fat embolism but the patient had not received the study drug infusion for three days prior to death	Low	Critical
Tinzaparin vs. placebo											

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
1 (Qari et al 2007)	randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	127	126	Tinzaparin treatment was associated with two minor bleeding events that were reported and treated by cessation of treatment	Low	Critical
Nitric oxide vs. placebo											
1 (Gladwin et al 2011)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[e]	None	8/75	6/75	RR 1.33 (CI 0.49, 3.66) for any serious adverse event including ACS, dysphagia, pyrexia and sensation of foreign body.	Low	Critical
Length of stay (LOS) in adults											
non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Adam-Graves et al 1997)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d,f,g]	Serious[c]	None	27	22	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 2002)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	126	123	MD = -4.00 hours (CI -25.23, 17.23)	Low	Critical
Vasodilator [isoxsuprine] vs. opioid [pethidine]											
1 (Al-Jama et al 1999)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	23	21	There was no significant difference in the median duration of	Low	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									hospitalisation in the isoxsuprine group (72 hours, range 24-288) compared to the meperidine group (72 hours, 24-216, p = 0.7)		
Tinzaparin vs. placebo											
1 (Qari et al 2007)	randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	127	126	MD = -4.98 days (CI -5.48, -4.48)	Low	Critical
Nitric oxide vs. placebo											
1 (Gladwin et al 2011)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[c]	None	75	75	There was no significant difference in the median length of hospitalisation in 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											
Nitric oxide vs. placebo											
1 (Gladwin et al 2011)	randomised trial	No serious risk of bias	No serious inconsistency	Serious[d]	Serious[e]	None	9/75	17/75	RR 0.53 (CI 0.25, 1.11)	Low	Important
Pain rating at 4 hours (assessed with: Visual Analogue Scale [VAS]) in children											
Nitric oxide vs. placebo											
1(Weiner et al 2003)	randomised trial	Serious[a]	No serious inconsistency	Serious[d]	Serious[c]	None	85	85	Overall mean change from baseline was -2.0 cm in the nitric oxide	Very low	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									group and -1.2 cm in the placebo group but this was not statistically significant (p = 0.37)		
Pain rating at 7 days (assessed with: Visual Analogue Scale [VAS]) in children											
non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Orringer[*] et al 2001)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	37	36	MD = -132.90 U/h (95% CI -345.83, 80.03)	Moderate	Critical
Amount of analgesia used in children											
IV methylprednisolone vs. IV placebo											
1 (Griffin et al 1994)	randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Serious[c]	None	23 (excluding patients requiring rescue analgesia)	23 (excluding patients requiring rescue analgesia)	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 to the placebo group respectively	Low	Critical
1 (Adawy et al 2005)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	15	15	MD (1 hour) = -0.30 cumulative morphine requirements (CI -1.11, 0.51) MD (2 hour) = -1.11 (CI -2.32, 0.10)	Moderate	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									MD (3 hour) = -2.00 (CI -3.57, -0.43)		
									MD (4 hour) = -2.27 (CI -4.24, -0.30)		
									MD (5 hour) = -2.70 (CI -5.07, -0.33)		
									MD (6 hour) = -2.95 (CI -5.51, -0.39)		
Non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Orringer et al 2003)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	37	36	MD (total analgesic use) = -0.19 MEU/kg (CI -0.47, 0.09)	Moderate	Critical
Oxygen vs. air											
1(Zipursky et al 1992)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	15	10	MD (mean hourly morphine dose) = 8.00 µ/k/h (CI -9.37, 25.37)	Moderate	Critical
Nitric oxide vs. placebo											
1 (Weiner et al 2003)	randomised trial	Serious[a]	No serious inconsistency	Serious[d]	Serious[c]	None	10	10	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	Very low	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									(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)		
Use of additional/rescue doses of analgesia in children											
IV methylprednisolone vs. placebo											
1 (Griffin et al 1994)	randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Serious[e]	None	26	30	RR 0.49 (CI 0.14, 1.72)	Low	Critical
1 (Adawy et al 2005)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	15	15	MD (mean rescue doses) = -0.95 mg (CI -1.70 to -0.20)	Moderate	Critical
Duration of painful episode in children											
Non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Orringer et al 2001)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	37	36	MD = -21.51 hours (CI -39.71, -3.31)	Moderate	Important
Xanthine derivative [pentoxiphyllin] vs. placebo											
Teuscher et al 1989	randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	18	18	MD = -24.80 hours (CI -46.74, -2.86)	Low	Important
Oxygen vs. air											
1 (Zipursky	randomised	No serious	No serious	No serious	Serious[c]	None	15	10	MD = 0.01 days [-0.89,	Moderate	Important

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
et al 1992)	trial	risk of bias	inconsistency	indirectness					0.91]		
Adverse events in children											
IV methylprednisolone vs. placebo											
1 (Adawy et al 2005)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[e]	None	15	15	There were significantly fewer events of nausea (2 vs. 9) and vomiting (0 vs. 7, $p < 0.05$) in the methylprednisolone group compared to the placebo group. There were no significant differences in the number of pruritus events (0 vs. 2).	Moderate	Critical
1 (Griffin et al 1994)	randomised trial	Serious[f]	No serious inconsistency	No serious indirectness	Serious[e]	None	26	30	No complications were observed during the study period related to corticosteroid use.	Low	Critical
Xanthine derivative [pentoxiphyllin] vs. placebo [saline]											
1 (Teuscher et al 1989)	randomised trial	Serious[a]	No serious inconsistency	No serious indirectness	Serious[e]	None	18	18	RR 2.00 (CI 0.59, 6.79) Adverse events were fever, shivering and pruritus	Low	Critical
Nitric oxide vs. placebo											
1 (Weiner et al 2003)	randomised trial	Serious[a]	No serious inconsistency	Serious[d]	Serious[e]	None	0/10	0/10	There were no episodes of hypotension, clinically significant SPO_2, toxic concentrations of NO_2 or clinically significant	Very low	Critical

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control			
									increases in methemglobin		
Length of stay (LOS) in children											
non-ionic surfactant [PP188] vs. placebo [saline]											
1 (Orringer et al 2002)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	37	36	MD = -3.98 hours (CI -43.22, 35.26)	Moderate	Critical
Oxygen vs. air											
1 (Zipursky et al 1992)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[c]	None	15	10	MD = 1.30 days (CI -1.13, 3.73)	Moderate	Critical
Nitric oxide vs. placebo											
1 (Weiner et al 2003)	randomised trial	Serious[a]	No serious inconsistency	Serious[d]	Serious[c]	None	10	10	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
Readmission within 48 hours in children											
IV methylprednisolone vs. placebo											
1 (Adawy et al 2005)	randomised trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[e]	None	0/15	0/15	No patients returned to ED within 48 hours	Moderate	Important

Quality assessment							No of patients		Measures of effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**			
Readmission within 2 weeks in children											
IV methylprednisolone vs. placebo											
1 (Griffin et al 1994)	randomised trial	Serious[†]	No serious inconsistency	No serious indirectness	Serious[e]	None	4/26	1/30	RR 4.62 (CI 0.55, 38.74)	Low	Important

[†] adjusted for baseline pain score
[a] Downgrade one level: unclear method of randomisation
[b] Downgrade one level: patient characteristics not reported at baseline
[c] Downgrade by one level: for continuous variables the imprecision criteria was downgraded if the 95% CI crosses the MID (the GDG agreed that this is 3 for pain ratings using a VAS scale and 2 days for length of stay) or if the total sample size is less than 400 (rule of thumb from GRADE)
[d] Downgrade by one level: population may have included both adults and children
[e] Downgrade by one level: for binary variables the imprecision criteria 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)
[f] minimum of 3 days stay in hospital required
[g] Downgrade by one level: no standardised analgesia
[h] Downgrade by one level: large proportion of younger patients were randomised to receive methylprednisolone

Review question 2: Non-pharmacological management

See full guideline for GRADE profile

Review question 3: Clinical signs and symptoms of acute complications

See full guideline for GRADE profile

Review question 4: Settings and skills for managing an acute painful episode

See full guideline for GRADE profile

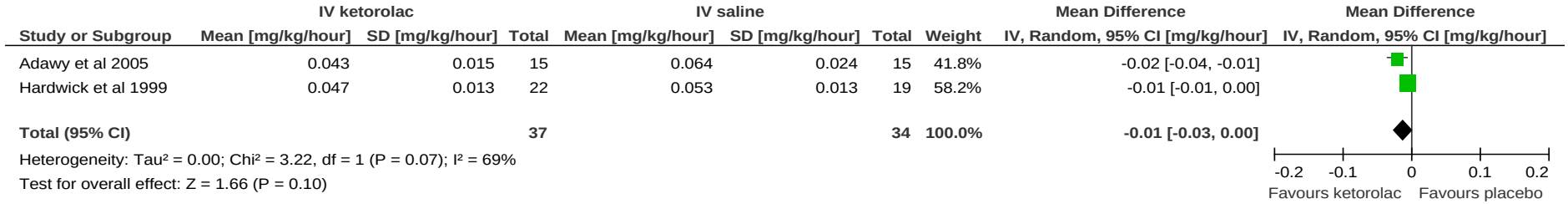
Review question 5: Information and support needs of patients and their carers during an acute painful sickle cell episode

No GRADE profile was completed. See full guideline for key themes matrix.

Forest plots

Review question 1: How should an acute painful sickle cell episode be managed using pharmacological interventions?

Figure 3 Forest plot of analgesic use in children treated with ketorolac vs. placebo



Critical appraisal checklist for a questionnaire study

Research question and study design	
Was a questionnaire the most appropriate method?	
Validity and reliability	
Have claims for validity been made, and are they justified? (Is there evidence that the instrument measures what it sets out to measure?)	
Have claims for reliability been made, and are they justified? (Is there evidence that the questionnaire provides stable responses over time and between researchers?)	
Format	
Are example questions provided?	
Did the questions make sense, and could the participants in the sample understand them? Were any questions ambiguous or overly complicated?	
Piloting	
Are details given about the piloting undertaken	
Was the questionnaire adequately piloted in terms of the method and means of administration, on people who were representative of the study population?	
Sampling	
Was the sampling frame for the definitive study sufficiently large and representative?	
Distribution, administration and response	
Was the method of distribution and administration reported	
Were the response rates reported, including details of participants who were unsuitable for the research or refused to take part?	
Have any potential response biases been discussed?	
Coding and analysis	
What sort of analysis was carried out and was this appropriate? (e.g. correct statistical tests for quantitative	

answers, qualitative analysis for open ended questions)	
Results	
Were all relevant data reported?	
Are quantitative results definitive (significant), and are relevant non-significant results also reported?	
Have qualitative results been adequately interpreted (e.g. using an explicit theoretical framework), and have any quotes been properly justified and contextualised?	
Conclusions and discussion	
Have the researchers drawn an appropriate link between the data and their conclusions?	
Have the findings been placed within the wider body of knowledge in the field (e.g. via a comprehensive literature review), and are any recommendations justified?	