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Sickle cell disease

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ABSTRACT

INTRODUCTION: Sickle cell disease causes chronic haemolytic anaemia, dactylitis, and painful acute crises. It also increases the risk of stroke, organ damage, bacterial infections, and complications of blood transfusion. In sub-Saharan Africa, up to a third of adults are carriers of the defective sickle cell gene, and 1% to 2% of babies are born with the disease. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: what are the effects of pharmaceutical and non-pharmaceutical interventions to prevent sickle cell crisis and other acute complications in people with sickle cell disease? What are the effects of pharmaceutical and non-pharmaceutical interventions to treat pain in people with sickle cell crisis? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 38 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: acupuncture, antibiotic prophylaxis in children <5 years of age, antibiotic prophylaxis in children >5 years of age, aspirin, avoidance of cold environment, blood transfusion, codeine, corticosteroid (with narcotic analgesics), diflunisal, hydration, hydroxyurea, ibuprofen, ketorolac, limiting physical exercise, malaria chemoprophylaxis, morphine (controlled-release oral after initial intravenous bolus, repeated intravenous doses), oxygen, paracetamol, patient-controlled analgesia, pneumococcal vaccines, and rehydration.

QUESTIONS

INTERVENTIONS

Key points

- In sub-Saharan Africa, up to a third of adults are carriers of the defective sickle cell gene, and 1% to 2% of babies are born with the disease.

  Sickle cell disease causes chronic haemolytic anaemia, dactylitis, and painful acute crises. It also increases the risk of stroke, organ damage, bacterial infections, and complications of blood transfusion.

- We don't know whether avoidance of cold environments, physical exercise, or rehydration can prevent crises or complications in people with sickle cell disease.

  Blood transfusion (prophylactic) reduces stroke in children at increased risk of stroke, but increases the risks of iron overload, allo-immunisation, hypertensive or circulatory overload, febrile non-haemolytic reactions, allergic reactions, and haemolytic events.

  Penicillin prophylaxis in children <5 years of age reduces invasive pneumococcal infections regardless of pneumococcal vaccination status. We don't know whether penicillin prophylaxis is beneficial in older children.

  Malaria chemoprophylaxis is considered useful in preventing malaria-induced crises, but we found few studies evaluating its benefit.

  Polyvalent polysaccharide pneumococcal vaccine does not reduce the incidence of pneumococcal infections in people with sickle cell disease. Pneumococcal conjugate vaccines have been reported to have protective efficacy in children <2 years of age, but this protective effect has not been shown in infants with sickle cell disease.

- Hydroxyurea may reduce some complications of sickle cell disease, such as painful crises compared with placebo, but long-term effects and safety are unknown.

- Morphine is widely used to treat severe pain, but we found no RCT evidence comparing it with placebo in people with sickle cell crises. Controlled-release oral morphine and patient-controlled analgesia may be as effective as repeated intravenous doses of morphine. Oral morphine increases the risk of acute chest syndrome compared with intravenous administration.

  High-dose corticosteroids may reduce the need for analgesia when added to intravenous morphine in people with a sickle cell crisis, but may increase the risks of adverse effects (such as infections, hypertension, and metabolic problems).

- It is still unclear whether acupuncture, blood transfusion, hydration, oxygen, aspirin, codeine, diflunisal, ibuprofen, ketorolac, or paracetamol reduce pain during sickle cell crisis.

DEFINITION

Sickle cell disease refers to a group of disorders caused by inheritance of a pair of abnormal haemoglobin genes, including the sickle cell gene. It is characterised by chronic haemolytic anaemia, dactylitis, and acute episodic clinical events called "crises". [1] Vaso-occlusive (painful) crises are the most common, and because of a resistance to nitric oxide, cause tissue ischaemia. Other crises are acute chest syndrome, sequestration crisis, and aplastic crisis. A common variant of sickle cell disease, also characterised by haemolytic anaemia, occurs in people with one sickle and one thalassaemia gene. **Sickle cell trait** occurs in people with one sickle gene and one normal gene. People with sickle cell trait have no clinical manifestation of illness. This review covers people with sickle cell disease with or without thalassaemia.

INCIDENCE/ PREVALENCE

Sickle cell disease is most common in people living in or originating from sub-Saharan Africa. [2] The disorder also affects people of Mediterranean, Caribbean, Middle-Eastern, and Asian origin. The sickle cell gene is most common in areas where malaria is endemic — sickle cell trait affects about 10% to 30% of Africa's tropical populations. [3] Sickle cell disease affects an estimated 1% to 2% (120,000) of infants in Africa annually. About 178 babies (0.28/1000 conceptions) are affected by sickle cell disease in England annually. [4] About 60,000 people in the US [4] and 10,000 in the UK suffer from the disease. [5]

AETIOLOGY/ RISK FACTORS

Sickle cell disease is inherited as an autosomal recessive disorder. For a baby to be affected both parents must have the sickle cell gene. In parents with sickle cell trait the risk of having an affected baby is 1 in 4 for each pregnancy. Painful (vaso-occlusive) crisis is the most common feature of the disease, and these episodes start in infancy and early childhood. [6] Factors that precipitate or modulate the occurrence of sickle cell crisis are not fully understood, but infections, hypoxia, dehydration, acidosis, stress (such as major surgery or childbirth), and cold are believed to play some role. In tropical Africa, malaria is the most common cause of anaemic and vaso-occlusive crisis. [3] High levels of fetal haemoglobin are known to ameliorate the severity and incidence of sickle cell crisis and other complications of the disease.

PROGNOSIS

People affected by sickle cell disease are predisposed to bacterial infections, especially those caused by encapsulated organisms such as *Pneumococcus*, *Haemophilus influenzae*, *Meningococcus*, and *Salmonella* species. Severe bacterial infections (such as pneumonia, meningitis, and

septicaemia) are common causes of morbidity and mortality, especially among young children. [7] About 10% of children with sickle cell anaemia may develop a stroke, and more than 50% of these may suffer recurrent strokes. [8] Abnormal features of cerebral blood vessels, shown by transcranial Doppler scan, predict a high risk of stroke in children with sickle cell disease. [9] Frequent episodes of crisis, infections, and organ damage reduce the quality of life of people with sickle cell disease. A high rate of vaso-occlusive (painful) crisis is an index of clinical severity that correlates with early death. Life expectancy remains low, especially in communities with poor access to health services. In some parts of Africa, about 50% of children with sickle cell disease die before their first birthday. [3] The average life expectancy with sickle cell disease in the US is about 42 years for men and about 48 years for women. [10] Frequent blood transfusions could increase the risk of immune reactions and infections, such as HIV and hepatitis B or C viruses, and Chagas' disease. The need for repeated blood transfusions in people with sickle cell disease predisposes them to the risk of iron overload. [11]

AIMS OF INTERVENTION

To reduce mortality, the incidence and severity of sickle cell crises, and other acute complications; to prevent organ damage; to improve quality of life and increase life expectancy; to achieve effective pain relief during crises with minimal adverse effects.

OUTCOMES

Mortality; **incidence of crisis**; **symptom severity** pain; **disease-related complications** dactylitis, incidence of other acute complications (e.g., malaria, stroke, infectious complications [invasive pneumococcal infection or acute osteomyelitis]); **quality of life**; **adverse effects** of treatment (e.g., gastrointestinal bleeding owing to NSAIDs, addiction to narcotic analgesics, immune reactions, and infections caused by blood transfusions [e.g., HIV, viral hepatitis, and Chagas' disease]). Secondary outcomes include duration of crisis, days out of school or work, and requirement for blood transfusion for severe anaemia. Fetal and total haemoglobin levels are considered proxy outcomes and are not addressed in this review.

METHODS

Clinical Evidence search and appraisal March 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2010, Embase 1980 to March 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this chapter were: published systematic reviews and RCTs in any language and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies, apart from the question on non-pharmaceutical interventions to prevent crisis and acute complications, where a minimum length of follow-up of 1 year was required. We included studies described as "open", "open label", or not blinded for this population. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. A search for published cohort studies was also undertaken for the avoidance of cold environment and limiting physical exercise interventions for the question on non-pharmaceutical interventions to prevent crisis and acute complications. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 18). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of non-pharmaceutical interventions to prevent sickle cell crisis and other acute complications in people with sickle cell disease?**

OPTION AVOIDANCE OF COLD ENVIRONMENT

We found no direct information from RCTs or observational studies about the effects of avoiding exposure to a cold environment on the prevention of sickle cell crisis and other life-threatening complications of sickle cell disease.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no RCTs or observational studies.

Comment: One 10-year retrospective study found a close correlation between cold weather and admissions for painful sickle cell crisis. [12] One observational study in 60 men with sickle cell disease and 30 adults with normal haemoglobin genotype found that vasoconstriction induced by skin cooling was significantly more likely to occur in people with sickle cell disease than in those with normal haemoglobin genotype (83% in people with sickle cell disease *v* 60% in people with normal haemoglobin genotype; P = 0.03). [13] Among people with sickle cell disease, the frequency of painful crises was significantly greater in those prone to cooling-induced vasoconstriction than in those less prone (0.36 crises/year in people prone to cooling-induced vasoconstriction *v* 0.12 crises/year in people less prone to cooling-induced vasoconstriction; P = 0.04). [13]

OPTION LIMITING PHYSICAL EXERCISE

We found no direct information from RCTs or observational studies about the effects of limiting exercise on prevention of sickle cell crisis and other life-threatening complications of sickle cell disease.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits: We found no systematic review, RCTs, or observational studies of sufficient quality.

Harms: We found no RCTs or observational studies.

Comment: **Clinical guide:**
Moderate exercise is generally accepted to be beneficial, especially in reducing the risk of cardio-vascular disease. Moderate exercise is, therefore, unlikely to cause harm in people with sickle cell disease. Strenuous exercise is suspected to lead to factors that may precipitate sickle cell crisis, such as low tissue oxygen saturation, dehydration, and stress.

OPTION REHYDRATION

We found no direct information from RCTs about the effects of increased fluid intake on the prevention of sickle cell crisis.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits: We found no systematic review or RCTs assessing increased fluid intake to prevent sickle cell crisis.

Harms: We found no RCTs.

Comment: People with sickle cell disease are more prone to dehydration because of hyposthenuria (reduced kidney ability to concentrate urine) leading to increased urine output. [14] Because dehydration leads to increased blood viscosity and acidosis, with the likely consequence of sickling and vaso-occlusion, increased fluid intake is routinely advocated for people with sickle cell disease.

OPTION BLOOD TRANSFUSION (PROPHYLACTIC) FOR SICKLE CELL CRISIS

Disease-related complications
Compared with standard care or no transfusion Blood transfusion given every 3 to 5 months is more effective at decreasing the incidence of stroke at 16 to 24 months in children with increased risk of stroke (high-quality evidence).

Mortality

Compared with standard care or no transfusion Blood transfusion given every 3 to 5 months is no more effective at reducing mortality in children with increased risk of stroke (high-quality evidence).

Adverse effects
Blood transfusion has been associated with a high risk of iron overload and allo-immunisation, hypertensive or circulatory overload, febrile non-haemolytic reactions, allergic reactions, and haemolytic events.

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits: We found one systematic review (search date 2009, 2 RCTs, 209 people). [15] The review found that, compared with standard care or no transfusion, prophylactic blood transfusion given every 3 to 5 months significantly reduced the incidence of stroke at 16 to 24 months in children with increased risk of stroke, as shown by abnormal transcranial Doppler scan (proportion who developed stroke: 1/101 [1%] with prophylactic transfusion *v* 13/108 [12%] with standard care; OR 0.10, 95% CI 0.02 to 0.58; P = 0.01). However, the review found no significant difference between groups in mortality (1/209 [1%] with transfusion *v* 0/209 [0%] with standard care or no transfusion; OR 3.32, 95% CI 0.31 to 84.01; P = 0.5).

Harms: The systematic review did not perform a meta-analysis for adverse effects. [15] However, it reported that the included trials found prophylactic transfusion was associated with a high risk of iron overload and allo-immunisation. One of the RCTs identified by the review reported that 10/63 (16%) children in the blood transfusion group with sickle cell disease developed allo-immunisation, but no other data were reported. [16] The RCT also reported 15 other transfusion-related adverse effects, including hypertension or circulatory overload (5 people), febrile non-haemolytic reactions (5 people), allergic reactions (3 people), and haemolytic events (2 people). [16] The review did not report data from adverse effects in the usual care control group of the trial. [15]

Another RCT included in the review also reported that iron overload developed faster than anticipated in the transfusion group, with mean serum ferritin levels rising from 164 ng/mL to 1804 ng/mL at 12 months, and to 2509 ng/mL at 24 months. The RCT did not report data for the control group. The RCT also found a new case (out of 35 people) of allo-immunisation in one person continuing transfusion, compared with no new cases in the discontinued transfusion group. [17] Although transmission of blood-borne infections is a widely recognised risk of a blood transfusion, none of the people involved in the reported trials acquired such infections.

Comment: None.

QUESTION What are the effects of pharmaceutical interventions to prevent sickle cell crisis and other acute complications in people with sickle cell disease?

OPTION ANTIBIOTIC PROPHYLAXIS IN CHILDREN <5 YEARS OF AGE

Disease-related complications
Penicillin compared with placebo Penicillin prophylaxis is more effective at reducing the risk of invasive pneumococcal infections in children aged <5 years with sickle cell disease. This beneficial effect is seen in children irrespective of their vaccination status (high-quality evidence).

Mortality
Penicillin compared with placebo Penicillin prophylaxis seems to be no more effective at reducing mortality in children aged <5 years with sickle cell disease (moderate-quality evidence).

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits: We found one systematic review (search date 2008, 2 RCTs, 457 children with sickle cell anaemia) comparing penicillin versus no penicillin or placebo. [18] The review found that penicillin prophylaxis caused a small but significant reduction in the risk of pneumococcal infections, regardless of vaccination status, compared with no penicillin or placebo (9/248 [4%] with penicillin prophylaxis *v* 19/209 [9%] without penicillin prophylaxis; RR 0.39, 95% CI 0.17 to 0.88). It found no significant difference in mortality between penicillin and no penicillin (0/105 [0%] with penicillin prophylaxis *v* 4/110 [4%] without penicillin prophylaxis; RR 0.12, 95% CI 0.01 to 2.14). [18] The wide confidence interval in the assessment of mortality suggests that the RCTs may have been underpowered to detect a difference in mortality.

The first RCT included in the review (242 children in Jamaica, aged 6–36 months) had a factorial design and compared monthly intramuscular penicillin injection (dose not reported) versus no injection. Half of the children receiving penicillin, and half of those not receiving penicillin, also received either polysaccharide pneumococcal vaccine or *Haemophilus influenza* vaccine. The second RCT

(215 children in the US, aged 3–36 months) compared oral penicillin (125 mg twice-daily) versus placebo. All children received polysaccharide pneumococcal vaccine at 1 and 2 years of age. The RCT was discontinued earlier than planned because of a highly significant reduction in the risk of pneumococcal infection in the penicillin group compared with the no penicillin group (RR 0.16, 95% CI 0.04 to 0.70), making it unethical to continue recruitment. [18]

Harms: One RCT identified by the review found minor adverse effects, including localised reactions to vaccine, and nausea and vomiting (3 cases); the difference in nausea and vomiting between penicillin prophylaxis and placebo was not significant (2/210 [0.95%] with penicillin prophylaxis *v* 1/199 [0.50%] without penicillin prophylaxis; RR 1.90, 95% CI 0.17 to 20.74). [18]

Comment: **Clinical guide:** Antibiotic prophylaxis and pneumococcal vaccines are recommended to reduce morbidity and mortality from pneumococcal infections in vulnerable groups, including children with sickle cell disease. [19] The effectiveness of antibiotic prophylaxis could be diminished by a high incidence of *Streptococcus pneumoniae* resistance. Allergy to penicillin is a contraindication. Erythromycin is usually the recommended alternative to penicillin, but its value in sickle cell disease has not been evaluated in an RCT.

OPTION ANTIBIOTIC PROPHYLAXIS IN CHILDREN >5 YEARS OF AGE

Disease-related complications
Penicillin compared with placebo Continuing penicillin prophylaxis for 2 years in children aged >5 years with sickle cell disease seems to be no more effective at reducing the risk of pneumococcal infections (moderate-quality evidence).

Mortality
Penicillin compared with placebo Continuing penicillin prophylaxis for 2 years in children aged >5 years with sickle cell disease seems to be no more effective at reducing mortality (moderate-quality evidence).

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits: We found one systematic review (search date 2008), [18] which identified one RCT (400 children with sickle cell anaemia, aged 5 years) comparing continuing penicillin prophylaxis after the age of 5 years versus placebo. [20] All of the children had received prophylactic penicillin for 2 years and polysaccharide pneumococcal vaccine at age 2 to 3 years. The RCT found no significant difference between continuing penicillin (125 mg twice-daily) and placebo in the risk of pneumococcal infections (RR 0.47, 95% CI 0.09 to 2.56) or mortality (RR 0.99, 95% CI 0.14 to 7.08).

Harms: The RCT reported nausea and vomiting both with penicillin and with placebo (nausea and vomiting: 2/201 [1.0%] with penicillin *v* 1/199 [0.5%] with placebo; significance not assessed). Local pain from the polysaccharide pneumococcal vaccine was also reported in two children. No serious adverse events were reported. [20]

Comment: **Clinical guide**:
See clinical guide in antibiotic prophylaxis in children <5 years of age, p 5 .

OPTION HYDROXYUREA

Incidence of crises
Compared with placebo Hydroxyurea is more effective at reducing the incidence of crises at 21 months in adults with sickle cell disease, and seems more effective at reducing admission to hospital and duration of hospital stay at 12 months in children (moderate-quality evidence).

Disease-related complications
Compared with placebo Hydroxyurea seems to be more effective at reducing the risk of acute chest syndrome, but seems to be no more effective at reducing the risk of stroke or hepatic sequestration in adults with sickle cell disease (moderate-quality evidence).

Mortality
Compared with placebo Hydroxyurea seems to be no more effective at reducing mortality in adults with sickle cell disease (moderate-quality evidence).

Quality of life
Compared with placebo Hydroxyurea seems to be no more effective at improving quality of life at 12 months in adults with sickle cell disease (moderate-quality evidence).

Adverse effects

Hydroxyurea has been associated with neutropenia, hair loss, skin rash, and gastrointestinal disturbances. We found no direct information from RCTs about the long-term effects of hydroxyurea.

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits:

Hydroxyurea versus placebo:
We found two systematic reviews (search date 2007), [21] [22] which between them identified two RCTs comparing hydroxyurea versus placebo. The first review [21] identified one parallel group RCT (299 adults) reported in two publications. [23] [24] It also found 6 further publications (subgroup analyses or follow-up studies) based on this RCT. The second review [22] identified one crossover RCT (25 children). [25]

Incidence of crises:
The RCT identified by the first review found that hydroxyurea significantly reduced the number of crises in adults compared with placebo after a mean follow-up of 24 months (299 adults, median number of painful crises per year: 2.5 with hydroxyurea *v* 4.5 with placebo; P <0.001). [21] The paediatric RCT identified by the second review found that, over 6 months, children taking hydroxyurea had significantly fewer hospital admissions and shorter hospital stays than children taking placebo (25 children, results after crossover: mean number of admissions per child: 12/22 [0.5%] with hydroxyurea *v* 31/22 [1.4%] with placebo; P = 0.0016; number of inpatient days per year: 7.1 days with hydroxyurea *v* 23.4 days with placebo; P = 0.0027). [22] [25]

Disease-related complications:
The RCT identified by the first review found that, at a mean follow-up of 24 months, hydroxyurea significantly reduced the risk of acute chest syndrome and the need for blood transfusion compared with placebo (299 adults; episodes of acute chest syndrome: 25 with hydroxyurea *v* 51 with placebo; P <0.001; proportion of patients requiring blood transfusion: 55/152 [36%] with hydroxyurea *v* 79/147 [54%] with placebo; P = 0.002). [21] It found no significant difference between hydroxyurea and placebo groups in strokes or hepatic sequestration (absolute numbers and significance not reported by review). [21]

Mortality:
The RCT identified by the first review found no significant difference between hydroxyurea and placebo in mortality related to sickle cell disease (absolute numbers and significance not reported by review). [21]

Quality of life:
The first review reported that the RCT (299 adults) found similar quality-of-life measures with hydroxyurea and placebo (absolute numbers and significance not reported by review). [21]

Harms:

The RCT (299 adults) identified by the first review found that bone marrow depression occurred more frequently with hydroxyurea compared with placebo (120/152 [79%] with hydroxyurea *v* 54/147 [37%] with placebo; significance not reported by review). [21] It also found more people with bleeding tendency with hydroxyurea compared with placebo (11/152 [7%] with hydroxyurea *v* 4/147 [3%] with placebo; significance not reported by review). It found similar rates of rash/nail changes, leg ulcers, fever, and aseptic necrosis in both treatment groups (rash/nail changes: 38/152 [25.0%] with hydroxyurea *v* 37/147 [25.2%] with placebo; leg ulcers: 23/152 [15%] with hydroxyurea *v* 25/147 [17%] with placebo; fever: 91/152 [60%] with hydroxyurea *v* 82/147 [56%] with placebo; aseptic necrosis: 14/152 [9.2%] with hydroxyurea *v* 13/147 [8.8%] with placebo; significance not reported by review). It found that fewer people receiving hydroxyurea experienced hair loss or lymphadenopathy compared with placebo (hair loss: 18/152 [12%] with hydroxyurea *v* 28/147 [19%] with placebo; lymphadenopathy: 68/152 [45%] with hydroxyurea *v* 82/147 [56%] with placebo; significance not reported by review). [21]

The crossover RCT (25 children), identified by the second review, found that thrombocytopenia occurred more frequently with hydroxyurea compared with placebo (2/25 [8%] with hydroxyurea *v* 0/25 [0%] with placebo; significance not reported). It also reported that there was no clinically significant toxicity. [22] [25]

Comment:

The adults in the RCT identified by the first review received the maximum tolerated dose of hydroxyurea or a maximum dose of 35 mg/kg daily. [21] One long-term observational follow-up study of the people in the RCT, identified by the first review, [21] concluded that adults taking hydroxyurea appeared to have reduced mortality after 9 years follow-up. It found that survival was related to fetal haemoglobin levels and frequency of vaso-occlusive events. [26]

The children in the RCT identified by the second review were treated with the maximum tolerated dose or a maximum of 25 mg/kg daily. [22]

The long-term safety of hydroxyurea in sickle cell disease remains uncertain.

OPTION MALARIA CHEMOPROPHYLAXIS

Incidence of crises
Compared with placebo Malaria chemoprophylaxis using proguanil or pyrimethamine seems to be more effective at reducing sickle cell crises in children (moderate-quality evidence).

Disease-related complications
Compared with placebo Malaria chemoprophylaxis using proguanil or pyrimethamine seems to be no more effective at reducing malaria infections in children (moderate-quality evidence).

Malaria chemoprophylaxis plus antibiotics compared with placebo Malaria chemoprophylaxis with chloroquine plus antibiotics may be more effective at reducing the incidence of malaria in areas without chloroquine resistance, but may be no more effective at reducing dactylitis (very low-quality evidence).

Note
Plasmodium falciparum malaria is believed to precipitate sickle cell crisis and to increase the risk of death in children with sickle cell anaemia. Regular chemoprophylaxis with antimalarial drugs is, therefore, advocated by consensus.

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits:

Malaria chemoprophylaxis versus placebo:
We found one systematic review (search date 2006, 1 RCT, 97 children; 1 quasi-randomised trial, 126 children). [27] The RCT identified by the review found that malaria chemoprophylaxis (proguanil or pyrimethamine) significantly reduced sickle cell crises compared with placebo (proportion with crisis: 2/68 [3%] with chemoprophylaxis *v* 5/29 [17%] with placebo; RR 0.17, 95% CI 0.04 to 0.83). It also found that chemoprophylaxis significantly reduced hospital admissions and blood transfusions (hospital admissions: 7/68 [10%] with chemoprophylaxis *v* 11/29 [40%] with placebo; RR 0.27, 95% CI 0.12 to 0.63; blood transfusions: 3/68 [4%] with chemoprophylaxis *v* 8/29 [27%] with placebo; RR 0.16, 95% CI 0.05 to 0.56). It found no significant difference between chemoprophylaxis and placebo in rates of malaria infection (19/68 [28%] with chemoprophylaxis *v* 9/29 [31%] with placebo; RR 0.90, 95% CI 0.46 to 1.75).

Malaria chemoprophylaxis plus antibiotic versus placebo:
The quasi-randomised trial identified by the review compared weekly malaria chemoprophylaxis using chloroquine plus antibiotic prophylaxis via a monthly injection of long-acting benzathine penicillin versus sterile water. [27] It found that malaria chemoprophylaxis plus antibiotics significantly reduced the incidence of malaria compared with sterile water (5/73 [7%] with chemoprophylaxis *v* 36/84 [43%] with sterile water; RR 0.16, 95% CI 0.07 to 0.39). It found no significant difference in dactylitis between malaria chemoprophylaxis plus antibiotics and sterile water (P <0.1; no further data reported). [27]

Harms:

The RCTs identified by the review gave no information on adverse effects. [27] The adverse effects of drugs commonly used for malaria prophylaxis (chloroquine, proguanil, doxycycline, mefloquine, and atovaquone–proguanil) are described elsewhere (see review on malaria: prevention in travellers).

Comment:

Inadequate allocation concealment and poor randomisation technique limit the validity of the results of the quasi-randomised trial identified by the review. [27] The RCT was performed between 1962 and 1964, at a time when chloroquine-resistant *P falciparum* was not as widespread as it is today.

Clinical guide:
Using chloroquine for malaria chemoprophylaxis in areas where chloroquine-resistance is known to be high is unlikely to be effective. Because *P falciparum* malaria is believed to precipitate sickle cell crisis and increase the risk of death in children with sickle cell anaemia, regular chemoprophylaxis with antimalarial drugs is advocated by consensus. [3]

OPTION PNEUMOCOCCAL VACCINES

Disease-related complications
Compared with placebo Polysaccharide pneumococcal vaccine is no more effective at reducing the incidence of pneumococcal infections in people with sickle cell disease (high-quality evidence).

Adverse effects
Both polysaccharide pneumococcal and pneumococcal conjugate vaccines (PCV) have been associated with mild fever, local pain, and swelling, but are not known to cause severe adverse effects.

For GRADE evaluation of interventions for sickle cell disease see **table, p 18** **.**

Benefits:

Polysaccharide pneumococcal vaccine versus placebo:
We found one systematic review (search date 2008, 1 RCT, 242 people). [28] The RCT identified by the systematic review found no significant difference in the incidence of pneumococcal infection between polysaccharide pneumococcal vaccination and placebo (AR: 11/159 [7%] with vaccination *v* 2/83 [2%] with placebo; RR 2.87, 95% CI 0.65 to 12.65). [28]

PCV versus placebo:
Three RCTs of PCV were identified by the review, but they did not assess clinical outcomes such as incidence of pneumococcal infections. [28]

Harms:

The systematic review found no severe adverse events with either polysaccharide pneumococcal or pneumococcal conjugate vaccines (PCVs), but both were associated with mild fever, local pain, and swelling. [28]

Comment:

Clinical guide:
Antibiotic prophylaxis and pneumococcal vaccines are recommended to reduce morbidity and mortality from pneumococcal infections in vulnerable groups, including children with sickle cell disease. [19] An increase in penicillin-resistant strains of *Streptococcus pneumoniae* has highlighted the potential for pneumococcal vaccination as an alternative to antibiotics. Polyvalent polysaccharide pneumococcal vaccine offers no protective immunity to children <2 years of age, who have the highest rates of invasive pneumococcal infections. [19] PCVs have been reported to have protective efficacy in children <2 years of age and are recommended for routine use in young children. However, this protective effect has not been shown in infants with sickle cell disease. [29]

QUESTION What are the effects of non-pharmaceutical interventions to treat pain in people with sickle cell crisis?

OPTION ACUPUNCTURE

We found no direct information from RCTs about the effects of acupuncture on pain in people with sickle cell disease.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits:

We found no systematic review or RCTs.

Harms:

Acupuncture is widely used to relieve pain. Adverse effects of acupuncture in different populations are discussed in other *Clinical Evidence* reviews (see reviews on acute low back pain and chronic low back pain).

Comment:

None.

OPTION HYDRATION

We found no direct information from RCTs about the effects of routinely giving extra fluids to reduce pain in people with sickle cell crises without dehydration.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits:

We found one systematic review (search date 2009) that identified no RCTs of sufficient quality assessing hydration in people with sickle cell disease. [30]

Harms:

We found no RCTs. [30]

Comment:

Clinical guide:
It is standard practice to give extra intravenous or oral fluids to dehydrated patients. This widely accepted clinical practice also applies to people with sickle cell disease who are dehydrated. However, it is unclear whether giving extra fluids routinely to people with painful sickle cell crisis without dehydration will be beneficial or harmful.

OPTION OXYGEN

Symptom severity (pain)

Compared with air We don't know whether oxygen given as an adjunct to continuous intravenous morphine is more effective at reducing pain or at reducing the progression of crises (appearance of new pain sites) in people with vaso-occlusive crisis (low-quality evidence).

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits:

Oxygen versus air:
We found no systematic review. One RCT (25 children and adolescents, aged 3–18 years with vaso-occlusive crisis) compared 50% oxygen versus air as an adjunct to continuous intravenous morphine infusion. [31] It found no significant difference in the duration of severe pain (0.94 days with 50% oxygen *v* 0.95 days with air; WMD –0.19 days, 95% CI –0.91 days to +0.89 days), amount of narcotic analgesic given, or further admission to hospital for pain (reported as non-significant for all outcomes; CI not reported). It also found no significant difference in the proportion of people with progression of crisis, indicated by the appearance of new pain sites (5/14 [35.7%] with 50% oxygen *v* 4/11 [36.4%] with air; reported as not significant; CI not reported). The RCT may have lacked power to detect a clinically important difference between interventions.

Harms:

Oxygen versus air:
The RCT gave no information about adverse effects associated with oxygen treatment. [31]

Comment:

The RCT was reported in two publications. [31] [32]

Clinical guide:
Low tissue-oxygen saturation is a dominant factor in the mechanism that results in sickling. Given that increased sickling is a key component of the pathophysiology of vaso-occlusive crisis and acute chest syndrome, oxygen treatment is expected to ameliorate these conditions. Oxygen treatment is recommended routinely for treatment of sickle cell acute chest syndrome, but people with acute chest syndrome were excluded from the RCT. [31]

OPTION BLOOD TRANSFUSION FOR SICKLE CELL PAIN

We found no direct information from RCTs about blood transfusions in the treatment of pain in sickle cell crisis.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits:

We found no systematic review or RCTs assessing blood transfusion to treat pain in sickle cell crisis.

Harms:

We found no RCTs.

Comment:

A systematic review showed (from limited evidence) that conservative pre-operative blood transfusion is as effective as aggressive transfusion in reducing the incidence of peri-operative complications in sickle cell disease. [33]

Clinical guide:
Repeated (chronic) blood transfusions are given to prevent severe complications of sickle cell disease, notably acute chest syndrome, sequestration crisis, and stroke, with some limited evidence of benefits. [15] [34] Blood transfusion is also used to treat acute chest syndrome of sickle cell disease with the aim of reducing the course of illness and risk of death. [34] [35] These interventions are associated with variable degrees of adverse events from repeated blood transfusions, such as infections, iron overload, allo-immunisation, and blood transfusion reactions (including delayed transfusion reactions and hyper-haemolytic syndrome). [14] [36] Decisions to use blood transfusion to treat or prevent any of the complications of sickle cell disease should take into account the need to balance benefits with harms.

QUESTION What are the effects of pharmaceutical interventions to treat pain in people with sickle cell crisis?

OPTION PATIENT-CONTROLLED ANALGESIA

Symptom severity (pain)
Compared with intermittently administered pethidine We don't know whether patient-controlled analgesia with pethidine is more effective at reducing pain at 3 days in adults with sickle cell crisis (low-quality evidence).

Compared with intermittently administered morphine Patient-controlled analgesia with high-dose and low-dose morphine may be no more effective at reducing pain in adults with sickle cell crisis (low-quality evidence).

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits:

Patient-controlled pethidine versus intermittently administered pethidine:
We found no systematic review. One RCT (20 adults, aged 17–39 years) compared patient-controlled analgesia (infusion of pethidine 25–30 mg/hour plus oral hydroxyzine 50 mg every 6 hours) versus intermittent intramuscular (im) analgesia (im pethidine 75–100 mg plus im hydroxyzine 50–75 mg given as necessary every 3–4 hours). [37] It found no significant difference between patient-controlled and intermittent analgesia in pain over 3 days, as measured by categorical and analogue pain scales (categorical scores on day 2: WMD +4.00 mm, 95% CI –1.09 mm to +9.09 mm; analogue scores: WMD +68.00 mm, 95% CI –25.35 mm to +161.35 mm). It also found no significant difference in the amount of pethidine used each day after 3 days (WMD +451 mg, 95% CI –70 mg to +972 mg). The units being measured in the pain scales were not defined.

Patient-controlled morphine versus intermittently administered morphine:
One RCT compared patient-controlled analgesia with morphine versus intermittent intravenous (iv) injections of morphine in two phases of high- and low-dose regimen in adults with sickle cell crisis pain. [38] In the first phase (20 people), the intermittent treatment group received a 4-mg iv bolus of morphine sulphate every 30 to 60 minutes, as needed, to achieve a linear analogue pain intensity score of <50 mm. The patient-controlled analgesia group received a 2-mg bolus of iv morphine sulphate followed by a 1-mg iv bolus controlled by the patient, with a 6-minute lockout. If pain control by the end of the first 30 minutes was inadequate (pain score <50 mm), the dose of morphine was increased to 6 mg for the intermittent treatment group, and to 1.5 mg for the patient-controlled analgesia group. The second phase (25 people) was similar, but used higher doses of morphine for the patient-controlled analgesia group (2.7 mg with a 10-minute lockout) and the intermittent treatment group (8 mg every 30–60 minutes). The RCT found a reduction in pain scores on the linear analogue scale in both groups, with no significant difference between treatment groups in both the first phase (WMD –0.10 mm, 95% CI –27.03 mm to +26.83 mm) and the second phase (WMD +9.00 mm, 95% CI –18.25 mm to +36.25 mm). It found no significant difference in the total amount of morphine given between patient-controlled analgesia and intermittent intravenous analgesia in the first phase (WMD –6.70 mg, 95% CI –23.35 mg to +9.95 mg) or the second phase of the study (WMD +6.40 mg, 95% CI –8.71 mg to +12.51 mg).

Harms:

Patient-controlled pethidine versus intermittently administered pethidine:
The RCT gave no information on adverse effects. [37] Severe adverse effects, such as seizures and respiratory depression, have been associated with pethidine. [39] There are concerns about possible addiction to narcotic analgesics, but some studies show a relatively low rate of addiction (0–11%) in people with sickle cell disease. [40]

Patient-controlled morphine versus intermittently administered morphine:
The RCT found that nausea, vomiting, and pruritus were common events observed with both high- and low-dose morphine, with 44% requiring antiemetic treatment (prochlorperazine) in the intermittent treatment group, and 31% requiring antiemetic treatment in the patient-controlled analgesia group. [38] The RCT found a non-significant difference in the proportion of people who had adverse effects (53% with patient-controlled analgesia *v* 47% with intermittent intravenous analgesia; P = 0.715), but no details were given about the types of adverse effects or their severity. Neither respiratory depression nor clinically significant hypotension were observed during the RCT. Respiratory depression is a well-known adverse effect of narcotic drugs.

Comment: None.

OPTION ASPIRIN

We found no direct information from RCTs about the effects of aspirin on pain in people with sickle cell disease.

For GRADE evaluation of other interventions for sickle cell disease see table, p 18 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment:

Clinical guide:
Aspirin is widely used by clinicians to relieve mild pain and fever. There is concern about its use in children as it has been associated with Reye's syndrome. The adverse effects of aspirin in different

populations are discussed in other *Clinical Evidence* reviews (see reviews on stroke prevention and NSAIDs). Studies on long-term aspirin prophylaxis address a different question on treating acute pain in sickle cell crisis to those here.

OPTION CODEINE

We found no direct information from RCTs about the effects of codeine on pain in people with sickle cell disease.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits: We found no systematic review or RCTs.

Harms: Codeine is widely used by clinicians to relieve moderate pain. Prolonged use of narcotic analgesics may lead to addiction. Codeine is known to be less addictive than other narcotic analgesics such as morphine and pethidine.

Comment: None.

OPTION DIFLUNISAL

Symptom severity (pain)
Compared with placebo We don't know whether diflunisal added to intramuscular pethidine regimens is more effective at reducing pain in people with vaso-occlusive sickle cell crisis (very low-quality evidence).

For GRADE evaluation of interventions for sickle cell disease see **table, p 18** **.**

Benefits: **Oral diflunisal versus placebo:**
We found one systematic review (search date 2002, 1 RCT, including 37 adults with sickle cell disease) comparing diflunisal versus placebo. [41] The RCT (37 adults, 32 having 46 episodes of vaso-occlusive crisis) compared oral diflunisal (22 adults, 1000 mg loading dose followed by 500 mg every 12 hours for 5 days) versus placebo (15 adults). [42] Intravenous pethidine (1.0–1.5 mg/kg) and hydroxyzine (0.5–1.0 mg/kg) were given every 3 to 4 hours as necessary for pain relief in all people. A categorical pain scale ranging from 0 to 5 was used to assess the response to treatment. The RCT found no significant difference in pain intensity scores between adding diflunisal and adding placebo (P reported as not significant; CI not reported). It also found no significant difference in the mean total dose of pethidine given (1400 mg with diflunisal *v* 1000 mg with placebo; WMD +400.0, 95% CI –28.6 to +828.6). The RCT is likely to have lacked power to detect a clinically important difference between treatments.

Harms: **Oral diflunisal versus placebo:**
The RCT found that diflunisal significantly increased nausea compared with placebo (6/22 [27%] with diflunisal *v* 2/15 [13%] with placebo; P <0.05). [42] One person discontinued diflunisal because of a facial rash. Adverse events associated with NSAIDs have been reviewed elsewhere in *Clinical Evidence* (see reviews on NSAIDs, acute low back pain, chronic low back pain, osteoarthritis of the knee, tennis elbow, and dysmenorrhoea).

Comment: The RCT used pain scales as the basis of randomised allocation. This method of randomisation may introduce bias.

OPTION IBUPROFEN

We found no direct information from RCTs about the effects of ibuprofen on pain in people with sickle cell disease.

For GRADE evaluation of other interventions for sickle cell disease see **table, p 18** **.**

Benefits: We found no systematic review or RCTs.

Harms: Ibuprofen is widely used by clinicians to relieve mild pain and fever. The adverse effects of ibuprofen in various populations are discussed in other *Clinical Evidence* reviews (see reviews on AOM, carpal tunnel syndrome, and migraine headache).

Comment: Adverse events associated with NSAIDs have been reviewed elsewhere in *Clinical Evidence* (see reviews on NSAIDs, acute low back pain, chronic low back pain, osteoarthritis of the hip, osteoarthritis of the knee, tennis elbow, and dysmenorrhoea).

OPTION KETOROLAC

Symptom severity (pain)

Compared with pethidine We don't know whether ketorolac is more effective at reducing pain in people with vaso-occlusive sickle cell crisis at 150 minutes (very low-quality evidence).

Ketorolac plus pethidine compared with placebo plus pethidine We don't know whether intravenous (iv) ketorolac given as a supplement to pethidine is more effective at reducing pain in people with vaso-occlusive sickle cell crisis (very low-quality evidence).

Ketorolac plus morphine sulphate compared with placebo plus morphine sulphate We don't know whether iv ketorolac plus parenteral morphine sulphate is more effective at reducing pain in people with vaso-occlusive sickle cell crisis (low-quality evidence).

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits: We found one systematic review (search date 2002, 4 RCTs, 88 people), [41] which identified 4 small RCTs comparing ketorolac versus placebo or other drugs. [43] [44] [45] [46] The review could not perform a meta-analysis owing to heterogeneity of the RCTs identified; individual RCTs are reported below.

Ketorolac versus pethidine:
One crossover RCT (20 adolescents, aged 11–19 years) compared parenteral ketorolac 1.0 mg/kg versus parenteral pethidine 1.5 mg/kg in sickle cell vaso-occlusive crisis in the first phase (150 minutes) before crossover. [43] Pain was measured in a visual analogue scale (VAS) ranging from 0 mm to 80 mm, where 0 mm denotes "no pain" and 80 mm denotes "the worst pain I've ever had". Measurements were taken at 30 and 150 minutes. It found that ketorolac significantly reduced pain compared with pethidine at 30 minutes (mean VAS: 39 mm with ketorolac *v* 54 mm with pethidine; P <0.01) and 150 minutes (mean VAS: 33 mm with ketorolac *v* 56 mm with pethidine; P <0.01). It found no significant difference between ketorolac and pethidine in the proportion of people who were pain free at 150 minutes (4/10 [40%] with ketorolac *v* 2/10 [20%] with pethidine; RR 2.00, 95% CI 0.47 to 8.56), but the RCT lacked power to detect clinically important differences. Data obtained after crossover were not included because the process of crossover is deemed unsuitable to confirm the effect of either drug.

Ketorolac plus pethidine versus placebo plus pethidine:
We found two RCTs. [44] [45] The first RCT (18 adults with vaso-occlusive sickle cell crisis) found no significant difference in pain between a single dose of intramuscular ketorolac 60 mg and placebo given as a supplement to repeated doses of iv pethidine (mean pain score assessed by VAS: 44 with ketorolac *v* 37 with placebo; P = 0.49). [44] The second RCT (21 people with sickle cell crisis >14 years of age) compared an iv infusion of ketorolac (150 mg on the first day, 120 mg on subsequent days for a total of 5 days) versus placebo as a supplement to intermittent intramuscular pethidine (100 mg every 3 hours for moderate or severe pain). [45] It found that people taking iv ketorolac required a significantly lower amount of pethidine to control pain compared with placebo (WMD –937.8 mg of pethidine, 95% CI –1803.2 mg to –72.4 mg).

Ketorolac plus morphine sulphate versus placebo plus morphine sulphate:
One RCT (29 people, 41 episodes of vaso-occlusive sickle cell crisis, aged 5–17 years) compared iv ketorolac 0.9 mg/kg versus placebo as a supplement to simultaneous treatment with parenteral morphine sulphate 0.1 mg/kg. [46] Morphine was repeated every 2 hours based on pain intensity rated on the VAS. Pain episodes were the basis for randomisation. The RCT found no significant difference in the need for morphine between ketorolac and placebo (0.28 mg/kg with ketorolac *v* 0.32 mg/kg with placebo; WMD –0.04 mg/kg, 95% CI –0.09 mg/kg to +0.01 mg/kg). It also found no significant difference between ketorolac and placebo in the proportion of people requiring admission for further management of severe pain (9/22 [41%] with ketorolac *v* 10/19 [53%] with placebo; RR 0.78, 95% CI 0.40 to 1.50).

Harms: No severe adverse events were reported in the RCTs, apart from one case of epistaxis in a person who received ketorolac. [45] Other adverse events (mostly gastrointestinal disturbances) were similar between treatment groups.

Comment: The RCTs used pain scales as the basis of randomised allocation. This method of randomisation may introduce bias.

OPTION PARACETAMOL

We found no direct information from RCTs about the effects of paracetamol (acetaminophen) on pain in people with sickle cell crisis.

Note
The FDA issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen) (August 2013).

For GRADE evaluation of other interventions for sickle cell disease see table, p 18 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.
Drug safety alert:
August 2013, paracetamol (acetaminophen) The Food and Drug Administration (FDA) has issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen). These skin reactions, known as Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP), can be fatal.(www.fda.gov/)

Comment: **Clinical guide:**
Paracetamol is widely used by clinicians to relieve mild pain and fever. Standard clinical dosage of paracetamol is well tolerated and unlikely to cause harm, but overdose is known to cause liver toxicity (see review on paracetamol [acetaminophen] poisoning).

OPTION CORTICOSTEROIDS

Symptom severity (pain)
Dexamethasone plus morphine compared with placebo We don't know whether intravenous (iv) dexamethasone given as an adjunct to narcotic analgesia is more effective at reducing pain in people with acute sickle cell episodes (very low-quality evidence).

Methylprednisolone plus morphine compared with placebo plus morphine We don't know whether high-dose iv methylprednisolone given as an adjunct to narcotic analgesia is more effective at reducing pain in people with acute episodes of severe sickle cell crisis (low-quality evidence).

Adverse effects
Corticosteroids have been associated with adverse effects such as increased risk of infections, weight gain, hypertension, poor glucose metabolism, cataracts, and poor growth in children.

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits: We found one systematic review (search date 2002, 3 RCTs, 148 people) [41] comparing corticosteroids plus narcotic analgesics versus placebo plus narcotic analgesics. Due to heterogeneity of methodologies and reporting, the review did not perform a meta-analyses. We, therefore, comment on all studies of sufficient quality individually below. We also found one additional RCT (38 children, median age 6.7 years) that compared dexamethasone versus placebo. [47]

Dexamethasone plus morphine versus placebo plus morphine:
One RCT included in the review (80 people randomised by sickle cell episodes, total of 152 acute sickle cell episodes) compared 2 days of parenteral dexamethasone (0.3 mg/kg/dose x 4 doses) versus placebo (saline) as an adjunct to analgesia. [48] The RCT found a significant reduction in the duration of analgesia therapy with dexamethasone compared with placebo (36.2 hours with dexamethasone *v* 48.4 hours with placebo; P = 0.04; CI not reported). [48] The additional RCT compared iv dexamethasone versus placebo, given as an adjunct to narcotic analgesia (iv morphine followed by oral codeine plus paracetamol) in 43 episodes of acute chest syndrome (34 children aged 1–13 years randomised on an individual level). It found that dexamethasone significantly reduced the need for analgesia when compared with placebo (mean number of analgesic doses: 2.5 with dexamethasone *v* 20.0 with placebo; P <0.001; mean duration of analgesic doses: 16.8 hours with dexamethasone *v* 76.8 hours with placebo; P <0.001). [47]

Methylprednisolone plus morphine versus placebo plus morphine:
The systematic review [41] identified one RCT comparing high-dose iv methylprednisolone versus placebo, given as an adjunct to narcotic analgesia (iv morphine followed by oral codeine plus paracetamol) in 56 acute episodes of severe painful sickle cell crisis in 34 people aged 2 to 19 years. Pain episodes were the basis for randomisation. [49] It found that methylprednisolone significantly reduced the duration of inpatient analgesia (iv or oral) compared with placebo (41.3 hours

with methylprednisolone *v* 71.3 hours with placebo; P = 0.01). It found no significant difference between methylprednisolone and placebo in re-admissions to hospital for recurrent pain within 2 weeks, although more people taking methylprednisolone were re-admitted (4/26 [15%] with methylprednisolone *v* 1/30 [3%] with placebo; RR 4.62, 95% CI 0.55 to 38.74). The RCT may have lacked power to rule out a clinically important difference between groups.

Harms:

Dexamethasone plus morphine versus placebo plus morphine:
The review gave no information on adverse effects. [41] Some known adverse effects of corticosteroids are increased risk of infections, weight gain, hypertension, poor glucose metabolism, cataracts, and poor growth in children.

Methylprednisolone plus morphine versus placebo plus morphine:
One RCT in the systematic review [41] found no adverse effects associated with methylprednisolone. [49]

Comment:

The RCTs used pain scales as the basis of randomised allocation. This method of randomisation may introduce bias.

OPTION MORPHINE

Symptom severity (pain)
Oral morphine compared with intravenous (iv) morphine Controlled-release oral morphine (given after an iv-loading dose of morphine at onset of treatment) and iv morphine are equally effective at reducing pain, and the duration of pain in children with vaso-occlusive crisis (moderate-quality evidence).

Adverse effects
Controlled-release oral morphine has been associated with an increased risk of acute chest syndrome in people with sickle cell crisis.

For GRADE evaluation of interventions for sickle cell disease see table, p 18 .

Benefits:

Morphine versus placebo:
We found no systematic review or RCTs.

Oral versus iv morphine:
We found one RCT (56 children, aged 5–17 years with painful crisis) comparing controlled-release morphine given orally (1.9 mg/kg every 12 hours) plus iv placebo (saline) versus iv morphine (0.04 mg/kg) plus placebo tablets for sickle cell vaso-occlusive crisis. [50] All children were given an iv-loading dose of morphine (0.15 mg/kg) at the onset of treatment. The RCT found that the oral medication was as effective as the iv injection. There was no significant difference in pain assessed by the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (WMD +0.10 units, 95% CI –0.09 units to +0.70 units) or other clinical pain scales (Oucher, faces, or clinical pain scales: –0.20 units, 95% CI –0.54 units to +0.14 units) throughout the observation period (at 09:00, 13:00, 17:00, and 21:00 hours every day). It also found no significant difference between oral and iv morphine in the mean frequency of rescue analgesia (WMD –0.12 doses/day, 95% CI –0.30 doses/day to +0.06 doses/day) and the mean duration of pain (WMD +1.20 days, 95% CI –0.01 days to +2.41 days).

Harms:

Oral morphine versus iv morphine:
The RCT found no significant difference in the frequency of spontaneously reported adverse events or severe-intensity events between oral and iv morphine (adverse events: 62% with oral morphine *v* 52% with iv morphine; severe-intensity events: 16% with oral morphine *v* 19% with iv morphine; no further significance assessment reported). Common adverse events were fever, pruritus, nausea, vomiting, and constipation; these did not differ significantly between study groups. [50] A post-hoc analysis of the same RCT found that oral morphine increased the risk of acute chest syndrome compared with iv morphine (AR: 12/21 [57%] with oral morphine *v* 4/23 [17%] with iv morphine; P <0.001; see comment below). [51]

Comment:

In the post-hoc analysis of the RCT, children with acute chest syndrome at enrolment were excluded. [51]

GLOSSARY

Aplastic crisis Sudden cessation of the bone marrow from making new blood cells.

CHEOPS scale (Children's Hospital of Eastern Ontario Pain scale) A behavioural scale used to evaluate postoperative pain. It was initially validated in children aged 1–5 years, and subsequently validated in children from other

populations and ages. [53] The CHEOPS scale is used to monitor the effectiveness of interventions for reducing pain and discomfort. Scores obtained from adding points from six different parameters range from 4 to 13.

Sequestration crisis Sudden pooling of blood in the spleen and liver, with the result that the person becomes anaemic and hypotensive, with the affected organ becoming remarkably enlarged and painful.

Acute chest syndrome A life-threatening complication of sickle cell disease characterised by fever, cough, chest pain, difficulty in breathing, worsening anaemia, and new pulmonary infiltrates on radiography. It is difficult to differentiate acute chest syndrome clinically from pneumonia and pulmonary infarctions.

Dactylitis Inflammation of the bones of the hands and feet, resulting in swelling, redness, and pain in the affected parts. It is common in young infants with sickle cell disease, and is precipitated by the sickle process that characterises sickle cell disease. Because it tends to occur bilaterally in the hands and feet with swelling of the dorsum, it is commonly described as sickle cell 'hand and foot syndrome'.

Fetal haemoglobin (Hb F) This is the predominant type of normal haemoglobin (i.e., the oxygen-carrying molecule in the human red blood cell) in the unborn child. Following birth, another type of normal haemoglobin (Hb A) replaces Hb F and remains predominant throughout life. Hb F binds oxygen more strongly than Hb A and maintains higher tissue oxygen tension than Hb A.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Pneumococcal conjugate vaccines Polysaccharide pneumococcal vaccines linked with proteins such as those of the outer membrane of meningococcus, tetanus, or diphtheria toxoids. The conjugate pneumococcal vaccines have been shown to be immunogenic in children younger than 2 years, and are recommended for routine use in infants beginning from the age of 2 months. [29] [52]

Polyvalent polysaccharide pneumococcal vaccine (PPV) This type of vaccine contains the purified capsular polysaccharides of several *Streptococcus pneumoniae* serotypes. Many of the polysaccharides contained in the vaccines do not induce protective immunity in children younger than 2 years. This type of pneumococcal vaccine is recommended for children aged 2 years and older affected by conditions that predispose them to an increased risk of invasive pneumococcal infection. [52]

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antibiotic prophylaxis in children <5 years of age for sickle cell crisis Search updated for already included systematic review. [18] No new evidence added. Categorisation unchanged (Beneficial).

Antibiotic prophylaxis in children >5 years of age Search updated for already included systematic review. [18] No new evidence added. Categorisation unchanged (Unknown effectiveness).

Blood transfusion (prophylactic) for sickle cell crisis Search updated for already included systematic review. [15] No new evidence added. Categorisation unchanged (Trade off between benefits and harms).

Hydration for sickle cell pain Search updated for already included systematic review. [30] No new evidence added. Categorisation unchanged (Unknown effectiveness).

Hydroxyurea New evidence added. [21] [22] Categorisation unchanged (Likely to be beneficial).

Pneumococcal vaccines for sickle cell crisis Search updated for already included systematic review. [28] No new evidence added. Categorisation unchanged (Unknown effectiveness).

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Disclaimer

TABLE GRADE evaluation of interventions for sickle cell disease

Important outcomes	Incidence of crises, disease-related complications, symptom severity (pain), quality of life, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of non-pharmaceutical interventions to prevent sickle cell crisis and other acute complications in people with sickle cell disease?									
2 (209) [15]	Disease-related complications	Blood transfusion (prophylactic) *v* standard care or no treatment	4	0	0	0	+1	High	Effect-size point added for OR <0.5
2 (209) [15]	Mortality	Blood transfusion (prophylactic) *v* standard care or no treatment	4	0	0	0	0	High	
What are the effects of pharmaceutical interventions to prevent sickle cell crisis and other acute complications in people with sickle cell disease?									
2 (457) [18]	Disease-related complications	Penicillin *v* placebo (children <5 years of age)	4	0	0	–1	+1	High	Directness point deducted for differences in vaccination status of children. Effect size point added for RR <0.5
2 (215) [18]	Mortality	Penicillin *v* placebo (children <5 years of age)	4	–1	0	0	0	Moderate	Quality point deducted for low event rates
1 (400) [18]	Disease-related complications	Penicillin *v* placebo (children >5 years of age)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (215) [18]	Mortality	Penicillin *v* placebo (children <5 years of age)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (324) [21] [22]	Incidence of crises	Hydroxyurea *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for results after crossover in one RCT.
1 (299) [21]	Disease-related complications	Hydroxyurea *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (299) [21]	Mortality	Hydroxyurea *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (299) [21]	Quality of life	Hydroxyurea *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (97) [27]	Incidence of crises	Malaria chemoprophylaxis *v* placebo	4	–1	0	–1	+1	Moderate	Quality point deducted for sparse data. Directness point deducted for uncertainty about generalisability of regimens used for prophylaxis. Effect size point added for RR < 0.5
1 (97) [27]	Disease-related complications	Malaria chemoprophylaxis *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (157) [27]	Disease-related complications	Malaria chemoprophylaxis plus antibiotic *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and randomisation/allocation flaws. Directness point deducted for uncertainty about generalisability of regimens used for prophylaxis
1 (242) [28]	Disease-related complications	Polysaccharide pneumococcal vaccine *v* control	4	0	0	0	0	High	
What are the effects of non-pharmaceutical interventions to treat pain in people with sickle cell crisis?									

Important outcomes	Incidence of crises, disease-related complications, symptom severity (pain), quality of life, mortality, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (50) [31]	Symptom severity (pain)	Oxygen *v* air	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of pharmaceutical interventions to treat pain in people with sickle cell crisis?									
1 (20) [37]	Symptom severity (pain)	Patient-controlled pethidine *v* intermittently administered pethidine	4	–2	0	0	0	Low	Quality points deducted for sparse data and uncertainty about method of evaluating pain
1 (45) [38]	Symptom severity (pain)	Patient-controlled morphine *v* intermittently administered morphine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (37) [41]	Symptom severity (pain)	Diflunisal *v* placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and randomisation/allocation flaws
1 (20) [41] [43]	Symptom severity (pain)	Ketorolac *v* pethidine	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and randomisation/allocation flaws. Consistency point deducted for different results at different endpoints
2 (39) [41] [44] [45]	Symptom severity (pain)	Ketorolac plus pethidine *v* placebo plus pethidine	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and randomisation/allocation flaws. Consistency point deducted for assessing different outcomes and for lack of agreement between studies
1 (29) [41] [46]	Symptom severity (pain)	Ketorolac plus morphine sulphate *v* placebo plus morphine sulphate	4	–2	0	0	0	Low	Quality points deducted for sparse data and randomisation/allocation flaws
2 (114) [47] [48]	Symptom severity (pain)	Dexamethasone plus morphine *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and randomisation/allocation flaws. Directness point deducted for not assessing pain reduction
1 (34) [41] [49]	Symptom severity (pain)	Methylprednisolone plus morphine *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and randomisation/allocation flaws
1 (86) [50]	Symptom severity (pain)	Oral morphine *v* intravenous morphine	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Type of evidence: 4 = RCT; 2 = observational.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.