Cochrane
Library

Cochrane Database of Systematic Reviews

Antibiotics for treating acute chest syndrome in people with sickle cell disease (Review)

Martí-Carvajal AJ, Conterno LO, Knight-Madden JM

Martí-Carvajal AJ, Conterno LO, Knight-Madden JM.

Antibiotics for treating acute chest syndrome in people with sickle cell disease.

Cochrane Database of Systematic Reviews 2015, Issue 3. Art. No.: CD006110.

DOI: 10.1002/14651858.CD006110.pub4.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	7
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	8
DATA AND ANALYSES	13
APPENDICES	13
WHAT'S NEW	14
HISTORY	15
CONTRIBUTIONS OF AUTHORS	16
DECLARATIONS OF INTEREST	16
SOURCES OF SUPPORT	16
INDEX TERMS	16

Antibiotics for treating acute chest syndrome in people with sickle cell disease

Arturo J Martí-Carvajal¹, Lucieni O Conterno², Jennifer M Knight-Madden³

¹Iberoamerican Cochrane Network, Valencia, Venezuela. ²Department of General Internal Medicine and Clinical Epidemiology Unit, Marília Medical School, Marília, Brazil. ³Sickle Cell Unit, Tropical Medicine Research Institute, Kingston 7, Jamaica

Contact address: Arturo J Martí-Carvajal, Iberoamerican Cochrane Network, Valencia, Venezuela. arturo.marti.carvajal@gmail.com.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2015.

Review content assessed as up-to-date: 6 March 2015.

Citation: Martí-Carvajal AJ, Conterno LO, Knight-Madden JM. Antibiotics for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2015, Issue 3. Art. No.: CD006110. DOI: 10.1002/14651858.CD006110.pub4.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The clinical presentation of acute chest syndrome is similar whether due to infectious or non-infectious causes, thus antibiotics are usually prescribed to treat all episodes. Many different pathogens, including bacteria, have been implicated as causative agents of acute chest syndrome. There is no standardized approach to antibiotic therapy and treatment is likely to vary from country to country. Thus, there is a need to identify the efficacy and safety of different antibiotic treatment approaches for people with sickle cell disease suffering from acute chest syndrome. This is an update of a Cochrane review first published in 2007, and previously updated in 2013.

Objectives

To determine whether an empirical antibiotic treatment approach (used alone or in combination):

1. is effective for acute chest syndrome compared to placebo or standard treatment;
2. is safe for acute chest syndrome compared to placebo or standard treatment;

Further objectives are to determine whether there are important variations in efficacy and safety:

3. for different treatment regimens,
4. by participant age, or geographical location of the clinical trials.

Search methods

We searched The Group's Haemoglobinopathies Trials Register, which comprises references identified from comprehensive electronic database searches and handsearching of relevant journals and abstract books of conference proceedings. We also searched the LILACS database (1982 to 23 February 2015), African Index Medicus (1982 to 23 February 2015), and the World Health Organization International Clinical Trials Registry Platform Search Portal (23 February 2015).

Date of most recent search of the Haemoglobinopathies Trials Register: 20 January 2015.

Selection criteria

We searched for published or unpublished randomised controlled trials.

Data collection and analysis

Each author intended to independently extract data and assess trial quality by standard Cochrane Collaboration methodologies, but no eligible randomised controlled trials were identified.

Main results

For this update, we were unable to find any randomised controlled trials on antibiotic treatment approaches for acute chest syndrome in people with sickle cell disease.

Authors' conclusions

This update was unable to identify randomised controlled trials on efficacy and safety of the antibiotic treatment approaches for people with sickle cell disease suffering from acute chest syndrome. Randomised controlled trials are needed to establish the optimum antibiotic treatment for this condition.

PLAIN LANGUAGE SUMMARY

Antibiotics for treating acute chest syndrome in people with sickle cell disease

Sickle cell disease affects millions of people throughout the world. Acute chest syndrome is a major cause of illness and death in people with sickle cell disease. Symptoms include fever, chest pain and a raised white blood cell count. Acute infection of the lung tissue is a major cause of acute chest syndrome. Antibiotics are often given to treat these lung infections, but there is no worldwide standard treatment. We searched for randomised controlled trials which compared antibiotics (alone or in combination) with other antibiotics, placebo or standard treatment. We wanted to know if the different antibiotic treatments were effective, if they were safe, and which doses worked best for acute chest syndrome in people with sickle cell disease. This update was unable to find any trials to include in this review. We conclude that a randomised controlled trial should attempt to answer these questions. Until there is firm evidence, clinicians should treat acute chest syndrome on a case by case basis and according to the diagnosis and the treatment available.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) was the first disease described at a molecular level (Pauling 1949). It results from a point mutation in the sixth codon of the gene which codes for the beta-globin chain resulting in hemoglobin S (HbS) (Bunn 1997). SCD is a group of genetic haemoglobin disorders which have their origins in sub-Saharan Africa and the Indian sub-continent. Population mobility has spread the disorders through Europe, Asia and the Americas. The term SCD includes sickle cell anaemia (Hb SS), haemoglobin S combined with hemoglobin C (Hb SC), haemoglobin S associated with β thalassaemia (S β 0 Thal and S β + Thal) and other double heterozygous conditions which cause clinical disease (Sauntharajah 2004; Steinberg 2009; Weatherall 2006). Haemoglobin S combined with normal hemoglobin (A) is known as sickle trait (AS), is asymptomatic and therefore not part of this

review. Significant morbidity and premature death result from SS disease with average life expectancy estimated at between 42 years and 53 years for men and between 48 and 58 years for women (Platt 1994; Wierenga 2001).

Although SCD is primarily a defect of red blood cells (a haematological defect), the changes in the blood red cells result in damage to blood vessels (vasculopathy) which is associated with chronic, progressive multi-organ damage (Aslan 2007; Hagar 2008; Kato 2007; Kato 2009a; Mack 2006; Morris 2008; Wood 2008). Acute, often life-threatening symptoms also occur, many of these in early life; childhood, adolescence, and early adulthood. The lungs are the site of both chronic damage (manifested as chronic sickle cell lung disease and pulmonary hypertension) and acute episodes (referred to as acute chest syndrome) (Benza 2008; Kato 2009b; Knight 1999; Serarslan 2009).

The term 'acute chest syndrome' (ACS) was coined by Charache (Charache 1979). He and his colleagues described 52 episodes of fever, chest pain, raised white blood cell count, and pulmonary infiltrates affecting 28 adults with sickle cell anaemia. Since then,

many narrative reviews of ACS have described its pathophysiology and epidemiology (Fauroux 1999; Johnson 2005; Mankad 2001). Papers from Poncz and Barret-Connors were important in establishing that ACS is in some cases caused by bacterial infection, viruses or atypical agents (Barrett-Connor 1971a; Barrett-Connor 1971b; Poncz 1985).

Acute chest syndrome can be defined as a new abnormal infiltrate (or shadow) on a chest radiograph, hypoxia (low blood oxygen concentration), constitutional upset and often one or more of the following symptoms: fever; cough; sputum production; rapid breathing (tachypnea); and breathing difficulties (dyspnea) (Vichinsky 2000). Different infectious pathogens are recognised as agents for developing episodes of ACS (Dean 2003; Lowenthal 1996; Neumayr 2003; Suara 2001; Vichinsky 2000). The rates of infections have been reported as: chlamydia, 7.2%; mycoplasma, 6.6%; and viruses, 6.4% (particularly respiratory syncytial virus (RSV) and *Streptococcus pneumoniae*, 4.3%) (Vichinsky 2000). Additionally, it has been reported that bacterial pneumonia may occur in up to 40% of cases of ACS (Davies 1984; Poncz 1985; van Agtmael 1994). Further causes of ACS include infarction due to thrombosis in situ, reported as the cause of ACS in 16.1% of episodes (Quinn 1999; Vichinsky 2000); blockage of the blood vessels in the lungs due to bone marrow fat embolism from bone marrow infarction (death of tissue due to acute obstruction to blood supply), reported as the cause in 8.8% of cases (Quinn 1999; Vichinsky 2000); and plate atelectasis resulting from lung splinting (reduction of lung or chest wall movement) (Lonergan 2001; Salzman 2002; Siddiqui 2003; Suell 2005). Additionally, an association with the development of ACS has been reported with endothelial dysfunction and nitric oxide metabolism (Sullivan 2008), opioids (Buchanan 2005; Kopecky 2004), asthma (Boyd 2004; Duckworth 2007; Nordness 2005; Knight-Madden 2005; Silvester 2007; Strouse 2008), abdominal surgery (Delatte 1999; Kokoska 2004; Wales 2001), free radicals (atoms or unpaired electrons) (Klings 2001), and smoking (Young 1992). Recently, genetic markers for an increased risk of ACS have been described (Mahdi 2009). This genetic diversity could help to explain the different epidemiological patterns in ACS morbidity and mortality (Alabdulaali 2007; Jaiyesimi 2007). In 48% of episodes, ACS developed during hospitalization for acute pain or other causes. A definite cause of ACS is established in only 38% of cases, but incomplete data precluded full assessment in 46% of cases (Johnson 2005; Vichinsky 2000). ACS increases the pulmonary pressures which enhances the risk of dying (Mekontso 2008).

The term ACS is applied because it is the clinical syndrome regardless of specific etiological factors in any particular person with this condition. Infection tends to predominate in children and infarction in adults as causative factors, but these two are often interrelated and concurrent (Wang 2004). Therefore, it can be seen that clinical presentation of ACS may be diverse (Taylor 2004; Vichinsky 2000). It has been suggested that it is appropriate to use an empirical approach in deciding initial antibiotic treatment

(Wang 2004).

Description of the intervention

The treatment approach for ACS usually includes oxygen and antibiotic therapy, with red blood cell transfusions as appropriate.

Why it is important to do this review

Antibiotic therapy in people with SCD and ACS is not standardized on a worldwide basis. The fact that different bacteria necessitate the use of different antibiotics leads to non-standardized therapy; different prescribing practices, drug availability, pathogen frequency and drug resistance in different countries may also contribute to this treatment diversity. This Cochrane Review therefore aims to determine the efficacy and safety of the various antibiotic treatment approaches for people with SCD suffering from ACS. This is an update of a Cochrane Review first published in 2007, and previously updated in 2013 (Martí-Carvajal 2007; Martí-Carvajal 2013).

See Glossary (Appendix 1).

OBJECTIVES

To determine whether an empirical antibiotic treatment approach (used alone or in combination):

1. is effective for ACS compared to placebo or standard treatment;
2. is safe for ACS compared to placebo or standard treatment.

To determine whether there are important variations in efficacy and safety:

3. for different treatment regimens,
4. by participant age, or geographical location of the clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized clinical trials (RCTs) irrespective of publication status (trials may be unpublished or published as an article, an abstract, or a letter), language (no language limitations will be applied) and country. We will include RCTs conducted in either a hospital or community setting, or both. No limits will be applied with respect to period of follow-up.

Types of participants

Men or women with SCD, (including sickle cell anaemia (Hb SS), sickle cell- β^0 -thalassaemia, Hb SC disease (Hb SC), and sickle cell- β^+ -thalassaemia), of any age, with ACS irrespective of cause. ACS was defined as a new infiltrate on chest radiograph with new-onset hypoxia associated with one or more symptoms, such as fever, cough, sputum production, tachypnea, dyspnea, or new-onset hypoxia irrespective of cause (Vichinsky 2000).

Types of interventions

We included comparative trials of antibiotics (used either alone or in combination), administered parenterally or orally and compared with another antibiotic, or placebo or standard treatment without antibiotics for treating ACS in people with SCD.

Types of outcome measures

Primary outcome

1. Mortality
 - i) Mortality related to ACS (if ACS was the underlying or immediate cause of death or played a major role in the cause of death)
 - ii) Mortality not related to ACS

Secondary outcomes

1. Respiratory failure rate: Hypoxemic respiratory failure defined as an arterial PO₂ of less than 60 mm Hg or hypercapnic respiratory failure (PCO₂ > 45 mm Hg) or both (Lee 2005).
2. Number of days of assisted ventilation.
3. Number of days to become afebrile.
4. Number of participants receiving red cell transfusion (simple or exchange).
5. Number of days using opioid analgesics.
6. Relapse rate, it will be defined as recurrence within six months of signs of ACS after improvement.
7. Number of days off work/school/normal daily activities related to the acute episode.

Adverse events

1. Adverse events: "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" (Nebeker 2004);
2. Adverse drug reactions: "a response to a drug which is noxious and uninitiated and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic functions" (Nebeker 2004).

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND acute chest syndrome.

The Haemoglobinopathies Trials Register was compiled from electronic searches of the Cochrane Central Register of Controlled Trials (Clinical Trials) (updated each new issue of *The Cochrane Library*) and weekly searches of MEDLINE. Unpublished work was identified by searching through the abstract books of four major conferences: the European Haematology Association conference; the American Society of Hematology conference; the Caribbean Health Research Council Meetings; and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the [Cystic Fibrosis and Genetic Disorders Group Module](#).

We also searched both the Latin American and Caribbean Health Sciences Information System (LILACS) database (1982 to 23 February 2015), [African Index Medicus](#): (1982 to 23 February 2015). Please refer to the appendices for further information on these search strategies ([Appendix 2](#); [Appendix 3](#)).

We also searched the [World Health Organization International Clinical Trials Registry Platform Search Portal](#) (23 February 2015). Please refer to an appendix for further information on this search strategy for detecting ongoing trials ([Appendix 4](#)).

Date of most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register: 20 January 2015.

Searching other resources

The bibliographic references of all retrieved literature were reviewed for additional reports of trials.

Data collection and analysis

We were unable to identify any randomised controlled trials eligible for inclusion in this review. Therefore, we could not perform the data analyses that we had planned. If, in the future, trials are identified and included in the review, we will adhere to the protocol described below:

Selection of studies

The three authors (AM, LC, JK) assessed each reference identified by searches to see if they meet the inclusion criteria. For the future update, We plan to resolve any disagreements that may arise through discussion.

Data extraction and management

Two authors will independently extract data from the selected trials using a standardised data extraction form (Zavala 2006) which is a web-based computer program allowing the easy transfer of extracted data into the RevMan software via a copy-paste function. Overall, we plan to extract data categorised into the following domains: demographics (such as age, sex, country in which RCT was performed), risk factors for ACS (such as haemoglobin level), phenotype (HbSS and HbSC), type of disease; cause of ACS; and variations in treatment regimens. We will follow recommendations from Cochrane Collaboration methodology and resolve any disagreements by consensus (Higgins 2011).

Assessment of risk of bias in included studies

Each review author will independently assess the risk of bias of each trial using a simple form and will follow the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will compare each review author assessment results and discuss any discrepancies between authors. We will achieve agreement on the final assessment for each criteria by discussion.

We will assess the following domains as either low, unclear or high risk of bias:

1. generation of the allocation sequence or randomisation;
2. concealment of allocation;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting;
6. other sources of bias (e.g. baseline imbalance, early

stopping) (Gurusamy 2009; Ioannidis 2008a; Ioannidis 2008b). We will use the following definitions.

Generation of the allocation sequence

- Low risk of bias: if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear risk of bias: if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- High risk of bias: if a system involving dates, names, or admittance numbers was used for the allocation of participants. These studies are known as quasi-randomised and will be excluded from the present review when assessing beneficial effects.

Allocation concealment

- Low risk of bias: if the allocation of participants involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.

- Unclear risk of bias: if the trial was described as randomised, but the method used to conceal the allocation was not described.
- High risk of bias: if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised. The latter will be excluded from the present review when assessing beneficial effects.

Blinding (or masking)

We will assess each trial (as low, unclear or high risk of bias) with regard to the following levels of blinding:

- blinding of clinician (person delivering treatment) to treatment allocation;
- blinding of participant to treatment allocation;
- blinding of outcome assessor to treatment allocation.

Incomplete outcome data

- Low risk of bias: the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear risk of bias: the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- High risk of bias: the number or reasons for dropouts and withdrawals were not described.

We will further examine the percentages of dropouts overall in each trial and per randomisation arm and we will evaluate whether intention-to-treat analysis has been performed or could be performed from the published information.

Selective outcome reporting

- Low risk of bias: adequate, pre-defined, or clinically relevant and reasonably expected outcomes are reported on.
- Unclear risk of bias: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

Other sources of bias

- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias, e.g., no sample size calculation made, early stopping, or an extreme baseline imbalance.

Results from these six domains will be summarized in a risk of bias tables. For each included RCT, the authors will review the evidence of bias in all domains, before reaching a judgement on the likely overall bias. These judgements will take into account the evidence of bias, the likely bias direction, and the likely bias magnitude, and will be stated explicitly.

Measures of treatment effect

For binary outcome measures (e.g. mortality, respiratory failure rate and relapse rate), we planned to estimate the relative risk (RR) with 95% confidence intervals (CI) for each outcome.

For all continuous outcomes (e.g. number of days of assisted ventilation, number of days to become afebrile, number of participants receiving red cell transfusion, number of days using opioid analgesics and number of days off work/school/normal daily activities related to the acute episode), we plan to record either mean change from baseline for each group or mean post-treatment or intervention values and their standard deviation or standard error for each group. We also plan to calculate a pooled estimate of treatment effect by calculating the weighted mean difference. If statistical details are missing (such as standard deviations), we will try to extract them from other relevant information in the paper, such as P values and with 95% CI

If insufficient data are available in published reports, we will contact the trial principal investigator.

Unit of analysis issues

We will examine continuous outcomes for skewness using the means and standard deviations as described in the Cochrane Handbook of Systematic Reviews for Interventions (Higgins 2011). If data are skewed, we will present log-transformed data.

Dealing with missing data

We will assess the percentages of dropouts overall for each included trial and by randomisation arm and we will evaluate whether an intention-to-treat analysis has been performed or could have been performed with the available published information.

In order to allow us to undertake an intention-to-treat analysis, we will seek data from the trial authors on the number of participants by treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

We will quantify statistical heterogeneity using the I^2 statistic, which describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). Moderate statistical heterogeneity is recognised for I^2 values of 30% or greater. We will consider there to be significant statistical heterogeneity if I^2 is greater than 30% (Higgins 2011).

Assessment of reporting biases

For future updates, we will also attempt to assess whether the review is subject to publication bias by using a funnel plot to graphically illustrate variability between trials. We will only do this

if at least 10 RCTs are included. If asymmetry is detected, causes other than publication bias will also be explored.

Data synthesis

If the eligible trials are sufficiently homogenous, we will summarize their findings using a fixed-effects model, if not (I^2 over 30%) we will use a random-effects model. Moreover, we accept that RCT clinical heterogeneity may mean that pooling of trials will not be possible. We will attempt to explain the cause of the heterogeneity according the Cochrane Handbook of Systematic Reviews for Interventions (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

In case of significant heterogeneity we will devote further research to identify possible causes of heterogeneity by exploring the impact of participant's characteristics.

We anticipate clinical heterogeneity for the following participant characteristics:

- SS type versus SC type;
- geographical location of RCT;
- participants' age;
- variations in treatment regimens.

We will explore these sources of heterogeneity in the assessment of the all outcomes by subgroup analyses, e.g. comparison of mild and severe disease and of participants on ventilatory support or not; comparison of disease type, i.e. SS type versus SC type; comparison of cause of ACS; comparison by country and within country; comparison of children with adults; comparison of use of antibiotic prophylaxis; comparison of use of antibiotic covering atypical agents; and comparison of route of antibiotic administration. These subgroup analyses will be only conducted for primary outcomes.

Sensitivity analysis

If sufficient trials are identified, we plan to conduct a sensitivity analysis comparing the results using all trials as follow:

1. RCTs with a low risk of bias (studies classified as having a 'low risk of bias' versus those identified as having a 'high risk of bias') (Higgins 2011).
2. RCTs that performed intention-to treat versus per-protocol analyses.

We will also evaluate the risk of attrition bias, as estimated by the percentage of participants lost. Trials with a total attrition of more than 30% or where differences between the groups exceed 10%, or both, will be excluded from meta-analysis but will be included in the review (Higgins 2011).

Summary of findings

We will use the principles of the GRADE system (Guyatt 2011) to assess the quality of the body of evidence associated with all main outcomes (Mortality, respiratory failure rate, number of days to become afebrile, number of days using opioid analgesics, number of participants receiving red cell transfusion (simple or exchange), number of days using opioid analgesics, and adverse events) table using the GRADE profiler software (GRADEPro 2008). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Evaluation of the quality of a body of evidence considers within study risk of bias, the directness of the evidence, heterogeneity in the data, precision of effect estimates and risk of publication bias (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g).

RESULTS

Description of studies

Results of the search

For previous versions of the review, 10 potentially relevant references were identified through the initial bibliographical searches (Martí-Carvajal 2007; Martí-Carvajal 2013). For this update, an additional 65 potentially relevant references were identified. After manually checking the titles and abstracts, none of the papers were regarded as eligible for further evaluation as they did not report on antibiotic therapy for ACS in SCD.

Included studies

No trials were included.

Excluded studies

No trials were identified.

Risk of bias in included studies

No trials were included.

Effects of interventions

The searches did not identify any randomised controlled trials eligible for inclusion in this systematic review, nor were we able to identify any ongoing trials.

DISCUSSION

Summary of main results

We have been unable to identify any clinical trials addressing the efficacy and safety of antibiotic treatment approaches for treating acute chest syndrome (ACS) in people with sickle cell disease (SCD). This is surprising in light of the number of people worldwide who suffer from this severe complication of SCD; ACS is an emergency in people with SCD.

Overall completeness and applicability of evidence

This Cochrane review did not find RCTs of antibiotics for treating ACS in people with SCD. Therefore, it was not possible to determine the efficacy and safety of the antibiotic treatment approaches (monotherapy or combined) for people with SCD suffering from ACS.

We have been unable to identify any clinical trials addressing the efficacy and safety of antibiotic treatment approaches for treating ACS in people with SCD; an emergency in this population. This is surprising in light of the number of people worldwide who suffer from this severe complication of SCD, and the strong link between infection, ACS, and SCD. ACS episodes predispose children to increased airway obstruction (Sylvester 2006).

There have been “three decades of innovation in the management of sickle cell disease” to improve the quality of treatment management for people with SCD (Bonds 2005), but no RCTs investigating the efficacy and safety of antibiotic treatment approaches for ACS in people with SCD have yet been conducted. This lack of trials shows a gap between clinical medicine and clinical investigation. Filling this gap may not be simple. It is unethical to withhold antibiotics in a situation where they may be life-saving, making a trial regarding the comparison of placebo with antibiotics unlikely in most clinical scenarios. Comparison of different antibiotic regimens, however, may be useful. This would require investigation of the cause of each ACS episode, including a search for a possible bacterial origin. Thus, to date, antibiotic choices remain pragmatic, based on available data regarding likely pathogens, local drug resistance patterns and the experience of the medical practitioner.

Due to functional asplenia, people with SCD are immunocompromised; therefore evidence from trials of antibiotics used to treat specific bacteria in people who do not have SCD may not be appropriate to extrapolate to people who do have SCD.

It is widely known that clinicians make practical decisions, often on the basis of inadequate information; decisions about treatment should be made based on the results of randomized trials (Chalmers 2004), but as Lottenberg states “The application of evidence-based medicine to the management of adults with SCD is

currently primarily driven by clinical expertise and patient preference, as there is a paucity of randomized controlled trial data to guide decision-making” (Lottenberg 2005). Acute chest syndrome in SCD is a good example; continuing clinical uncertainty does not benefit patients and may increase health-service costs (Alderson 2000). We hope that this review clarifies the clinical uncertainty and so encourages further research (Alderson 2000). The paucity of data on antibiotic treatment for ACS in people with SCD should stimulate the development of well-planned randomised trials in an attempt to evaluate the widespread empirical practice of treating ACS in people with SCD.

Quality of the evidence

RCTs were not found on this clinical issue.

Potential biases in the review process

The main limitation of this Cochrane Review is the paucity of evidence in people with SCD suffering from ACS. Our exhaustive search of published and unpublished randomized controlled trials was not able to find any registered completed trials.

Agreements and disagreements with other studies or reviews

There are no other reviews or studies to compare with this Cochrane review.

AUTHORS' CONCLUSIONS

Implications for practice

This updated Cochrane Review found no randomised controlled trials of antibiotics in people with sickle cell disease suffering acute chest syndrome. Therefore, it was not possible to determine the efficacy and safety of the antibiotic treatment approaches (used either alone or in combination) for people with SCD suffering from ACS. Hence, we recommend that until evidence becomes available, clinicians continue to treat patients on a case-by-case basis given the diagnosis and treatments available to them.

Implications for research

This Cochrane Review has identified the need for well-designed, adequately-powered randomised controlled trials to assess the benefits and harms of antibiotic treatment approaches (used either alone or in combination) as a way of improving the survival and decreasing mortality from ACS in people with SCD.

Future trials regarding this issue should be planned according to the recommendations of 'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) (Chan 2013a; Chan 2013b), and reported according to the 'Consolidated Standards of Reporting Trials' (CONSORT) statement for improving the quality of reporting of efficacy and to get better reports of harms in clinical research (Ioannidis 2004; Moher 2010; Turner 2012), and the Foundation of Patient-Centered Outcomes Research (Basch 2012; Gabriel 2012).

ACKNOWLEDGEMENTS

To Mrs Nikki Jahnke, and Miss Tracey Remington from the Cochrane Cystic Fibrosis & Genetic Disorders Group for their help and editorial advice during preparation of this review.

To Dr Ian Hambleton and peer reviewers for their comments to enhance the quality of this review.

REFERENCES

Additional references

Alabdulaali 2007

Alabdulaali MK. Sickle cell disease patients in eastern province of Saudi Arabia suffer less severe acute chest syndrome than patients with African haplotypes. *Annals of Thoracic Medicine* 2007;**2**:158–62.

Alderson 2000

Alderson P, Roberts I. Should journals publish systematic reviews that find no evidence to guide practice? Examples from injury research. *BMJ* 2000;**320**(7231):376–7.

Aslan 2007

Aslan M, Freeman BA. Redox-dependent impairment of vascular function in sickle cell disease. *Free Radical Biology & Medicine* 2007;**43**:1469–83.

Balshem 2011

Balshem H, Helfand M, Schunemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of Clinical Epidemiology* 2011; **64**(4):401–6. [PUBMED: 21208779]

Barrett-Connor 1971a

Barrett-Connor E. Acute pulmonary disease and sickle cell anemia. *The American Review of Respiratory Disease* 1971;

104:159–65.

Barrett-Connor 1971b

Barrett-Connor E. Bacterial infection and sickle cell anemia. An analysis of 250 infections in 166 patients and a review of the literature. *Medicine (Baltimore)* 1971;**50**:97–112.

Basch 2012

Basch E, Aronson N, Berg A, Flum D, Gabriel S, Goodman SN, et al. Methodological standards and patient-centeredness in comparative effectiveness research: the PCORI perspective. *JAMA* 2012;**307**(15):1636–40.

Benza 2008

Benza RL. Pulmonary hypertension associated with sickle cell disease: pathophysiology and rationale for treatment. *Lung* 2008;**186**:247–54.

Bonds 2005

Bonds DR. Three decades of innovation in the management of sickle cell disease: the road to understanding the sickle cell disease clinical phenotype. *Blood Review* 2005;**19**: 99–110.

Boyd 2004

Boyd JH, Moinuddin A, Strunk RC, DeBaun MR. Asthma and acute chest in sickle-cell disease. *Pediatric Pulmonology* 2004;**38**:229–32.

Buchanan 2005

Buchanan ID, Woodward M, Reed GW. Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. *Pediatric Blood & Cancer* 2005;**45**:716–24.

Bunn 1997

Bunn HF. Pathogenesis and treatment of sickle cell disease. *New England Journal of Medicine* 1997;**337**:762–9.

Chalmers 2004

Chalmers I. Well informed uncertainties about the effects of treatments. How clinicians and patients respond?. *BMJ* 2004;**328**(7438):475–6.

Chan 2013a

Chan AW, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;**346**: e7586.

Chan 2013b

Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine* 2013;**158**(3):200–7.

Charache 1979

Charache S, Scott JC, Charache P. “Acute chest syndrome” in adults with sickle cell anemia. Microbiology, treatment, and prevention. *Archives of Internal Medicine* 1979;**139**: 67–9.

Davies 1984

Davies SC, Luce PJ, Win AA, Riordan JF, Brozovic M. Acute chest syndrome in sickle-cell disease. *Lancet* 1984; **323**(8367):36–8.

Dean 2003

Dean D, Neumayr L, Kelly DM, Ballas SK, Kleman K, Robertson S, et al. Chlamydia pneumoniae and acute chest syndrome in patients with sickle cell disease. *Journal of Pediatric Hematology/Oncology* 2003;**25**(1):46–55.

Delatte 1999

Delatte SJ, Hebra A, Tagge EP, Jackson S, Jacques K, Othersen HB Jr. Acute chest syndrome in the postoperative sickle cell patient. *Journal of Pediatric Surgery* 1999;**34**: 188–91.

Duckworth 2007

Duckworth L, Hsu L, Feng H, Wang J, Sylvester JE, Kissoon N, et al. Physician-diagnosed asthma and acute chest syndrome: associations with NOS polymorphisms. *Pediatric Pulmonology* 2007;**42**:332–8.

Fauroux 1999

Fauroux B, Tamalet A, Desmarquest P, Clement A. Pathophysiology of acute thoracic syndrome. *Pathologie-biologie* 1999;**47**:26–30.

Gabriel 2012

Gabriel SE, Normand SL. Getting the Methods Right - The Foundation of Patient-Centered Outcomes Research. *New England Journal of Medicine* 2012;**367**(9):787–90. [PUBMED: 22830434]

GRADEPro 2008 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro. Version 3.2 for Windows. McMaster University, 2008.

Gurusamy 2009

Gurusamy KS, Gluud C, Nikolova D, Davidson BR. Assessment of risk of bias in randomized clinical trials in surgery. *The British Journal of Surgery* 2009;**96**:342–9.

Guyatt 2011

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93.

Guyatt 2011a

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. *Journal of Clinical Epidemiology* 2011;**64**(12):1294–302.

Guyatt 2011b

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of Clinical Epidemiology* 2011;**64**(12):1277–82.

Guyatt 2011c

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. *Journal of Clinical Epidemiology* 2011;**64**(12):1303–10.

Guyatt 2011d

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up

- the quality of evidence. *Journal of Clinical Epidemiology* 2011;**64**(12):1311–6.
- Guyatt 2011e**
Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). *Journal of Clinical Epidemiology* 2011;**64**(4):407–15.
- Guyatt 2011f**
Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383–94.
- Guyatt 2011g**
Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**(4):380–2.
- Hagar 2008**
Hagar W, Vichinsky E. Advances in clinical research in sickle cell disease. *British Journal of Haematology* 2008;**141**: 346–56.
- Higgins 2003**
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.
- Higgins 2011**
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
- Ioannidis 2004**
Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine* 2004;**141**(10): 781–8.
- Ioannidis 2008a**
Ioannidis JP. Why most discovered true associations are inflated. *Epidemiology* 2008;**19**:640–8.
- Ioannidis 2008b**
Ioannidis JP. Perfect study, poor evidence: interpretation of biases preceding study design. *Seminars in Hematology* 2008;**45**:160–6.
- Jaiyesimi 2007**
Jaiyesimi O, Kasem M. Acute chest syndrome in Omani children with sickle cell disease: epidemiology and clinical profile. *Annals of Tropical Paediatrics* 2007;**27**:193–9.
- Johnson 2005**
Johnson CS. The acute chest syndrome. *Hematology/Oncology Clinics of North America* 2005;**19**(5):857–79.
- Kato 2007**
Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Reviews* 2007;**21**:37–47.
- Kato 2009a**
Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: Biology, pathophysiology, genetics, translational medicine, and new research directions. *American Journal of Hematology* 2009;**84**: 618–25.
- Kato 2009b**
Kato GJ, Wang Z, Machado RF, Blackwelder WC, Taylor JG 6th, Hazen SL. Endogenous nitric oxide synthase inhibitors in sickle cell disease: abnormal levels and correlations with pulmonary hypertension, desaturation, haemolysis, organ dysfunction and death. *British Journal of Haematology* 2009;**145**:506–13.
- Klings 2001**
Klings ES, Farber HW. Role of free radicals in the pathogenesis of acute chest syndrome in sickle cell disease. *Respiratory Research* 2001;**2**:280–5.
- Knight 1999**
Knight J, Murphy TM, Browning I. The lung in sickle cell disease. *Pediatric Pulmonology* 1999;**28**:205–16.
- Knight-Madden 2005**
Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. *Thorax* 2005;**60**:206–10.
- Kokoska 2004**
Kokoska ER, West KW, Carney DE, Engum SE, Heiny ME, Rescorla FJ. Risk factors for acute chest syndrome in children with sickle cell disease undergoing abdominal surgery. *Journal of Pediatric Surgery* 2004;**39**:848–50.
- Kopecky 2004**
Kopecky EA, Jacobson S, Joshi P, Koren G. Systemic exposure to morphine and the risk of acute chest syndrome in sickle cell disease. *Clinical Pharmacology and Therapeutics* 2004;**75**(3):140–6.
- Lee 2005**
Lee WL, Slutsky AS. Hypoxemic Respiratory Failure, Including Acute Respiratory Distress Syndrome. *Murray & Nadel's Textbook of Respiratory Medicine*. Saunders, 2005.
- Loneragan 2001**
Loneragan GJ, Cline DB, Abbondanzo SL. Sickle cell anemia. *Radiographics* 2001;**21**:971–94.
- Lottenberg 2005**
Lottenberg R, Hassell KL. An evidence-based approach to the treatment of adults with sickle cell disease. *Hematology / The Education Program of the American Society of Hematology*. American Society of Hematology. Education Program, 2005:58–65.
- Lowenthal 1996**
Lowenthal EA, Wells A, Emanuel PD, Player R, Prchal JT. Sickle cell acute chest syndrome associated with parvovirus B19 infection: case series and review. *American Journal of Hematology* 1996;**51**:207–13.

Mack 2006

Mack AK, Kato GJ. Sick cell disease and nitric oxide: a paradigm shift?. *The International Journal of Biochemistry & Cell Biology* 2006;**38**:1237–43.

Mahdi 2009

Mahdi N, Al-Subaie AM, Al-Ola K, Al-Irhayim AQ, Ali ME, Al-Irhayim Z, et al. HLA DRB1*130101-DQB1*060101 haplotype is associated with acute chest syndrome in sickle cell anemia patients. *Tissue Antigens* 2009;**73**:245–9.

Mankad 2001

Mankad VN. Exciting new treatment approaches for pathophysiologic mechanisms of sickle cell disease. *Pediatric Pathology & Molecular Medicine* 2001;**20**:1–13.

Mekontso 2008

Mekontso Dessap A, Leon R, Habibi A, Nzouakou R, Roudot-Thoraval F, Adnot S, et al. Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. *American Journal of Respiratory and Critical Care Medicine* 2008;**177**:646–53.

Moher 2010

Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. *Journal of Clinical Epidemiology* 2010;**63**(8):e1–37. [PubMed: 20346624]

Morris 2008

Morris CR. Mechanisms of vasculopathy in sickle cell disease and thalassemia. *Hematology / the Education Program of the American Society of Hematology*. Philadelphia: American Society of Hematology, 2008:177–85.

Nebeker 2004

Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Annals of Internal Medicine* 2004;**140**:795–801.

Neumayr 2003

Neumayr L, Lennette E, Kelly D, Earles A, Embury S, Groncy P, et al. Mycoplasma disease and acute chest syndrome in sickle cell disease. *Pediatrics* 2003;**112**(1 Pt 1):87–95.

Nordness 2005

Nordness ME, Lynn J, Zacharisen MC, Scott PJ, Kelly KJ. Asthma is a risk factor for acute chest syndrome and cerebral vascular accidents in children with sickle cell disease. Clinical and molecular allergy: CMA [electronic resource] 2005; Vol. 3:2.

Pauling 1949

Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. *Science* 1949;**110**:543–6.

Platt 1994

Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *New England Journal of Medicine* 1994;**330**:1639–44.

Poncz 1985

Poncz M, Kane E, Gill FM. Acute chest syndrome in sickle cell disease: etiology and clinical correlates. *Journal of Pediatrics* 1985;**107**:861–6.

Quinn 1999

Quinn CT, Buchanan GR. The acute chest syndrome of sickle cell disease. *Journal of Pediatrics* 1999;**135**:416–22.

Salzman 2002

Salzman SH. Does splinting from thoracic bone ischemia and infarction contribute to the acute chest syndrome in sickle cell disease?. *Chest* 2002;**122**:6–9.

Sauntharajah 2004

Sauntharajah Y, Vichinsky EP, Embury SH. Sickle cell disease. *Hoffman: Hematology: Basic Principles and Practice*. Churchill Livingstone, 2004.

Serarslan 2009

Serarslan G, Akgül F, Babayigit C. High prevalence of pulmonary hypertension in homozygous sickle cell patients with leg ulceration. *Clinical and Experimental Hypertension* 2009;**31**:44–8.

Siddiqui 2003

Siddiqui AK, Ahmed S. Pulmonary manifestations of sickle cell disease. *Postgraduate Medical Journal* 2003;**79**(933):384–90.

Silvester 2007

Sylvester KP, Patey RA, Broughton S, Rafferty GF, Rees D, Thein SL, et al. Temporal relationship of asthma to acute chest syndrome in sickle cell disease. *Pediatric Pulmonology* 2007;**42**:103–6.

Steinberg 2009

Steinberg MH. Genetic etiologies for phenotypic diversity in sickle cell anemia. *The Scientific World Journal* 2009;**9**:46–67.

Strouse 2008

Strouse JJ, Takemoto CM, Keefer JR, Kato GJ, Casella JF. Corticosteroids and increased risk of readmission after acute chest syndrome in children with sickle cell disease. *Pediatric Blood & Cancer* 2008;**50**:1006–12.

Suara 2001

Suara RO. Group A beta-haemolytic streptococcal acute chest event in a child with sickle cell anaemia. *Annals of Tropical Paediatrics* 2001;**21**:175–8.

Suell 2005

Suell MN, Bezold LI, Okcu MF, Mahoney DH Jr, Shardonofsky F, Mueller BU. Increased pulmonary artery pressures among adolescents with sickle cell disease. *Journal of Pediatric Hematology/Oncology* 2005;**27**:654–58.

Sullivan 2008

Sullivan KJ, Kissoon N, Gauger C. Nitric oxide metabolism and the acute chest syndrome of sickle cell anemia. *Pediatric Critical Care Medicine* 2008;**9**:159–68.

Sylvester 2006

Sylvester KP, Patey RA, Milligan P, Rafferty GF, Broughton S, Rees D, et al. Impact of acute chest syndrome on lung

- function of children with sickle cell disease. *Journal of Pediatrics* 2006;**149**:17–22.
- Taylor 2004**
Taylor C, Carter F, Poulouse J, Rolle S, Babu S, Crichlow S. Clinical presentation of acute chest syndrome in sickle cell disease. *Postgraduate Medical Journal* 2004;**80**:346–9.
- Turner 2012**
Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.MR000030.pub2]
- van Agtmael 1994**
van Agtmael MA, Cheng JD, Nossent HC. Acute chest syndrome in adult Afro-Caribbean patients with sickle cell disease. Analysis of 81 episodes among 53 patients. *Archives of Internal Medicine* 1994;**154**:557–61.
- Vichinsky 2000**
Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *New England Journal of Medicine* 2000;**342**:1855–65.
- Wales 2001**
Wales PW, Carver E, Crawford MW, Kim PC. Acute chest syndrome after abdominal surgery in children with sickle cell disease: Is a laparoscopic approach better?. *Journal of Pediatric Surgery* 2001;**36**(5):718–21.
- Wang 2004**
Wang WC. Unstable Hemoglobin Disease. In: Greer JP, Foerster J, Lukens JN, Rogers GM, Frixos P, Glader BE editor(s). *Wintrobe's Clinical Hematology*. 11th Edition. Lippincott Williams & Wilkins, 2003.
- Weatherall 2006**
Weatherall D, Akinyanju O, Fucharoen S, Olivieri N, Musgrove P. Inherited Disorders of Hemoglobin. *Disease Control Priorities in Developing Countries*. 2nd Edition. Washington DC: The World Bank and Oxford University Press, 2006.
- Wierenga 2001**
Wierenga KJ, Hambleton IR, Lewis NA. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based population study. *Lancet* 2001;**357**(9257): 680–3.
- Wood 2008**
Wood KC, Hsu LL, Gladwin MT. Sickle cell disease vasculopathy: a state of nitric oxide resistance. *Free Radical Biology and Medicine* 2008;**44**:1506–28.
- Young 1992**
Young RC Jr, Rachal RE, Hackney RL Jr, Uy CG, Scott RB. Smoking is a factor in causing acute chest syndrome in sickle cell anemia. *Journal of the National Medical Association* 1992;**84**:267–71.
- Zavala 2006 [Computer program]**
Zavala D, Martí A, Peña-Martí G, Comunián G. Sheet to enter data for performing a Cochrane review. Version 1. Valencia, Venezuela: Universidad de Carabobo, 2006.

References to other published versions of this review

- Martí-Carvajal 2007**
Martí-Carvajal AJ, Conterno LO, Knight-Madden JM. Antibiotics for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD006110.pub2; MEDLINE: 17443613]
- Martí-Carvajal 2013**
Martí-Carvajal AJ, Conterno LO, Knight-Madden JM. Antibiotics for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD006110.pub3]

* Indicates the major publication for the study

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Glossary

Term	Definition	Source
Anemia, Sickle Cell	A disease characterized by chronic hemolytic anemia, episodic painful crises, and pathologic involvement of many organs. It is the clinical expression of homozygosity for hemoglobin S	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)
Anti-Bacterial Agents	Substances that reduce the growth or reproduction of bacteria	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)
Acute chest syndrome	Respiratory syndrome characterized by the appearance of a new pulmonary infiltrate on chest x-ray, accompanied by symptoms of fever, cough, chest pain, tachypnea, or dyspnea, often seen in patients with sickle cell anemia. Multiple factors (e.g., infection, and pulmonary fat embolism) may contribute to the development of the syndrome	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)
Hemoglobin, Sickle	An abnormal hemoglobin resulting from the substitution of valine for glutamic acid at position 6 of the beta chain of the globin moiety. The heterozygous state results in sickle cell trait, the homozygous in sickle cell anemia	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)
Hemoglobin SC Disease	One of the sickle cell disorders characterized by the presence of both hemoglobin S and hemoglobin C. It is similar to, but less severe than sickle cell anemia	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)
Sickle Cell Trait	The condition of being heterozygous for hemoglobin S.	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)
Tachypnea	Increased respiratory rate.	MeSH (Medical Subject Headings). National Library of Medicine (http://www.ncbi.nlm.nih.gov/mesh)

Appendix 2. Search strategy and results: LILACS searched 1982 to 23 February 2015

Strategy	Results	# Included studies
(Sickle AND Acute chest syndrome) AND (((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535\$ OR (Tw clin\$ AND (Tw trial\$ OR Tw ensa\$ OR Tw estud\$ OR Tw experim\$ OR Tw investiga\$)) OR (Tw singl\$ OR Tw simple\$ OR Tw doubl\$ OR Tw doble\$ OR Tw duplo\$ OR Tw trebl\$ OR Tw trip\$) AND (Tw blind\$ OR Tw cego\$ OR Tw ciego\$ OR Tw mask\$ OR Tw mascar\$)) OR Mh placebos OR Tw placebo\$ OR (Tw random\$ OR Tw randon\$ OR Tw casual\$ OR Tw acaso\$ OR Tw azar OR Tw aleator\$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337\$ OR Mh follow-up studies OR Mh prospective studies OR Tw control\$ OR Tw prospectiv\$ OR Tw volunt\$ OR Tw volunteer\$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))))	22	0

Appendix 3. African Index Medicus (up to 23 February 2015)

Sickle AND acute chest syndrome

Results: 17 references.

Included studies: none.

Appendix 4. World Health Organization. International Clinical Trials. Registry Platform Search Portal (23 February 2015)

Sickle AND acute chest syndrome AND antibiotics.

Results: 138 references.

Included: none.

WHAT'S NEW

Last assessed as up-to-date: 6 March 2015.

Date	Event	Description
6 March 2015	New citation required but conclusions have not changed	Minor revisions to the review have been made throughout.
6 March 2015	New search has been performed	A total of 65 potentially eligible references were identified by the searches; however, none were eligible for inclusion in the review

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 2, 2007

Date	Event	Description
24 January 2013	Amended	Contact details updated.
2 November 2012	New citation required but conclusions have not changed	The updated version contains minor changes throughout the text
2 November 2012	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register was undertaken but found no trials eligible for inclusion in the review
28 July 2011	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register was undertaken but found no trials eligible for inclusion in the review
11 November 2009	Amended	The following sections of the review have been amended in line with latest Cochrane guidelines: 1. Background 2. Methods 3. Discussion
11 November 2009	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no new references eligible for inclusion in this review

(Continued)

30 October 2008	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register identified no new references eligible for inclusion in this review
11 April 2008	Amended	Converted to new review format.
20 February 2008	New search has been performed	<p>A search of the Group's Haemoglobinopathies Trials Register identified no references which were eligible for inclusion in this review.</p> <p>We have updated the original 'Synopsis' with a new 'Plain language summary' in line with the latest guidance from The Cochrane Collaboration</p>

CONTRIBUTIONS OF AUTHORS

Arturo Martí-Carvajal conceived and drafted the review with comments from Lucieni Conterno and Jennifer Knight-Madden.

Arturo Martí-Carvajal acts as guarantor for the review.

DECLARATIONS OF INTEREST

In 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'How to critically appraise clinical trials on osteoporosis and how to teach this'. This activity was not related to his work with the Cochrane Collaboration or any Cochrane Review.

In 2007 Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop 'How to critically appraise clinical trials and how to teach this'. This activity was not related to his work with the Cochrane Collaboration or any Cochrane Review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Iberoamerican Cochrane Centre, Spain.
Academic.

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Chest Syndrome [*drug therapy; microbiology]; Anti-Bacterial Agents [*therapeutic use]; Cough [drug therapy]; Fever [*drug therapy]; Hypoxia [*drug therapy]; Sputum [secretion]

MeSH check words

Humans