Cochrane
Library

Cochrane Database of Systematic Reviews

Antibiotics for treating community-acquired pneumonia in people with sickle cell disease (Review)

Martí-Carvajal AJ, Conterno LO

Martí-Carvajal AJ, Conterno LO.
Antibiotics for treating community-acquired pneumonia in people with sickle cell disease.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD005598.
DOI: [10.1002/14651858.CD005598.pub4](https://doi.org/10.1002/14651858.CD005598.pub4).

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	4
METHODS	4
RESULTS	7
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	8
REFERENCES	9
APPENDICES	13
WHAT'S NEW	16
HISTORY	16
CONTRIBUTIONS OF AUTHORS	17
DECLARATIONS OF INTEREST	17
SOURCES OF SUPPORT	17
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	17
INDEX TERMS	17

[Intervention Review]

Antibiotics for treating community-acquired pneumonia in people with sickle cell disease

Arturo J Martí-Carvajal¹, Lucieni O Conterno²¹Facultad de Ciencias de la Salud Eugenio Espejo, Universidad UTE (Cochrane Ecuador), Quito, Ecuador. ²Medical School, Department of Internal Medicine, Infectious Diseases Division, State University of Campinas (UNICAMP), Campinas, Brazil**Contact address:** Arturo J Martí-Carvajal, arturo.marti.carvajal@gmail.com.**Editorial group:** Cochrane Cystic Fibrosis and Genetic Disorders Group.**Publication status and date:** Edited (no change to conclusions), published in Issue 9, 2020.**Citation:** Martí-Carvajal AJ, Conterno LO. Antibiotics for treating community-acquired pneumonia in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2016, Issue 11. Art. No.: CD005598. DOI: [10.1002/14651858.CD005598.pub4](https://doi.org/10.1002/14651858.CD005598.pub4).

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

As a consequence of their condition, people with sickle cell disease are at high risk of developing an acute infection of the pulmonary parenchyma called community-acquired pneumonia. Many different bacteria can cause this infection and antibiotic treatment is generally needed to resolve it. 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 community-acquired pneumonia. This is an update of a previously published Cochrane Review.

Objectives

To determine the efficacy and safety of the antibiotic treatment approaches (monotherapy or combined) for people with sickle cell disease suffering from community-acquired pneumonia.

Search methods

We searched The Group's Haemoglobinopathies Trials Register (01 September 2016), which comprises references identified from comprehensive electronic database searches and handsearching of relevant journals and abstract books of conference proceedings. We also searched LILACS (1982 to 01 September 2016), African Index Medicus (1982 to 20 October 2016) and WHO ICT Registry (20 October 2016).

Selection criteria

We searched for published or unpublished randomized controlled trials.

Data collection and analysis

We intended to summarise data by standard Cochrane methodologies, but no eligible randomized controlled trials were identified.

Main results

We were unable to find any randomized controlled trials on antibiotic treatment approaches for community-acquired pneumonia in people with sickle cell disease.

Authors' conclusions

The updated review was unable to identify randomized controlled trials on efficacy and safety of the antibiotic treatment approaches for people with sickle cell disease suffering from community-acquired pneumonia. Randomized controlled trials are needed to establish the optimum antibiotic treatment for this condition. The trials regarding this issue should be structured and reported according to the

CONSORT statement for improving the quality of reporting of efficacy and improved reports of harms in clinical research. Trialists should consider including the following outcomes in new trials: number of days to become afebrile; mortality; onset of pain crisis or complications of sickle cell disease following community-acquired pneumonia; diagnosis; hospitalization (admission rate and length of hospital stay); respiratory failure rate; and number of participants receiving a blood transfusion.

There are no trials included in the review and we have not identified any relevant trials up to September 2016. We therefore do not plan to update this review until new trials are published.

PLAIN LANGUAGE SUMMARY

Antibiotics for treating pneumonia caught outside of hospital or care homes in people with sickle cell disease

Review question

We reviewed the evidence on the effect and safety of the antibiotic treatment approaches (one drug alone or combined drugs) for people with sickle cell disease with from community-acquired pneumonia. This is an update of a previously published Cochrane Review.

Background

Sickle cell disease affects millions of people throughout the world. These people can catch pneumonia more easily due to sickle damage to the spleen. The germs causing pneumonia caught in the community vary across the world. They have different sensitivities and resistance levels which are affected by how antibiotics are prescribed in that area.

Search date

The evidence is current to: 01 September 2016.

Study characteristics

We were not able to find any trials to include in this review.

Key results

Trials addressing this issue should be structured and reported according to the CONSORT statement for improving the quality of reporting of efficacy and improved reports of harms in clinical research. Trial investigators should consider including the following outcomes in new trials: number of days to be free of fever, death, onset of pain crisis or complications of sickle cell disease following community-acquired pneumonia, diagnosis, hospitalization (admission rate and length of hospital stay), respiratory failure rate, and number of participants receiving a blood transfusion. Since no trials have been included in the review up until September 2016, we will still search for trials every two years, but will not publish an updated version of this review until any eligible trials are identified.

BACKGROUND

See glossary for definitions of medical terms ([Appendix 1](#)).

Description of the condition

Sickle cell disease (SCD) was the first disease described at a molecular level ([Pauling 1949](#)). It is a lifelong inherited disease and the most common haemoglobinopathy ([Ballas 2010](#); [Orkin 2010](#); [Rees 2010](#)). Recently, the history and others aspects of SCD have been reviewed ([Mousa 2010](#); [Prabhakar 2010](#); [Serjeant 2010](#)).

Sickle cell anaemia affects millions of people throughout the world, it is regarded as a public health priority by the World Health Organization (WHO) ([Makani 2011](#)). Globally, over 330,000 affected infants are born with haemoglobin disorders annually, of them 83% are born with sickle cell disorders ([Modell 2008](#)). An estimated 70% of sufferers live in Africa ([Makani 2007](#)). It is particularly common among people whose ancestors come from Sub-Saharan Africa, South America, Cuba, Central America, Saudi Arabia, India, and Mediterranean countries such as Turkey, Greece, and Italy ([Makani 2011](#); [Stuart 2004](#); [Weatherall 2006](#)). In the United States of America, it affects around 72,000 people, most of whose ancestors come from Africa. The disease occurs in about one in every 500 African-American births and one in every 1000 to 1400 Hispanic-American births. Approximately two million Americans, or one in 12 African-Americans, carry the sickle cell allele ([Loureiro 2005](#); [WHO 2005](#)). Prevalence for the sickle cell gene is as high as 25% to 30% in western Africa ([Fleming 1989](#)).

The term SCD includes sickle cell anaemia (Hb SS), haemoglobin S combined with haemoglobin C (Hb SC), haemoglobin S associated with β Thalassemia (S β 0 Thal and S β + Thal) and other less prevalent double heterozygous conditions which cause clinical disease ([Steinberg 2009](#); [Weatherall 2006](#)). Haemoglobin S combined with normal haemoglobin (A) is known as the sickle cell trait (AS), which is generally asymptomatic and is not part of this review.

Although SCD is primarily a hematological defect, the changes in the blood red cells lead to vasculopathy associated with progressive multiorgan damage ([Hebbel 2004](#); [Wood 2008](#)). The spleen and lung are two of the target organs in this population. People with SS will develop functional asplenia (hypoactivity and finally atrophy of the spleen; splenic hypofunction) ([Begue 2001](#); [Lane 1995](#); [Zago 1983](#)); this leads to frequent and often severe infections which are produced by encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*) ([Beytout 2003](#); [Castagnola 2003](#); [Melles 2004](#); [Vichinsky 2000](#); [Waghorn 2001](#)). The physiopathology of the immune impairment due to hyposplenia is multifactorial ([Chanet 2004](#)); immunoglobulin M (IgM) memory B cells that are responsible for the protection against infections by encapsulated bacteria, require the spleen for their generation and survival ([Di Sabatino 2005](#)).

The two major forms of clinical lung involvement in SCD are acute chest syndrome (ACS) and sickle cell chronic lung disease (pulmonary fibrosis, pulmonary hypertension and cor pulmonale) ([Maitre 2011](#); [Vij 2010](#)). Both of these are associated with significant morbidity and mortality ([Castro 2005](#); [Knight 1999](#); [Machado 2005](#); [Siddiqui 2003](#)). Acute chest syndrome in SCD is defined by the triad of hypoxaemia, lung infiltrates on X-ray and

systemic upset ([Castro 1994](#); [Golden 1998](#); [Siddiqui 2003](#); [Stuart 2001](#); [Vichinsky 2000](#)). There are a variety of causes including infection, plate atelectasis resulting from lung splinting, vaso-occlusion and thromboembolism. Infections, such as pneumonia, can worsen SCD because local or systemic hypoxia increases sickle haemoglobin (Hb S) polymerisation ([NIH 2002](#)).

People with SCD have a susceptibility to pneumonia ([Battersby 2010](#)) as a consequence of sickle damage to the spleen ([Waterer 2005](#)), and are at high risk of developing an acute infection with encapsulated bacteria that can involve the pulmonary parenchyma (proven by growth from blood or sputum and antibody levels). This is called community-acquired pneumonia (CAP), when associated with at least some symptoms of acute infection and accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds or localized rales or both) in an individual not hospitalised or residing in a long-term care facility for more than 14 days before onset of symptoms ([Begue 2001](#); [WHO 2004](#)). Platelet-activating factor receptor regulation is associated with an increased risk of invasive pneumococcal disease in people with SCD ([Miller 2007](#)).

People with SCD can get infections with any respiratory pathogen. In those with concomitant lung disease as a consequence of SCD, other infections may have a greater impact, especially influenza, where the inflammation that results from acute infection may exacerbate that which is pre-existing and further complicate the disease ([Dean 2003](#); [Neumayr 2003](#); [Vichinsky 1997](#); [Vichinsky 2000](#)).

In the USA, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae* are more common as infectious agents of CAP ([Dean 2003](#); [Haas 2005](#); [Neumayr 2003](#); [Vichinsky 2000](#)). In people with SCD aged 10 years and older other causes of bacteraemia include *Staphylococcus aureus*, salmonella, enterobacter, *Hemophilus influenzae*, and clostridia ([Vichinsky 1997](#)).

Description of the intervention

Based on the above, antibiotic therapy (monotherapy or in combination) in people with SCD suffering from CAP is not standardized worldwide. The fact that different bacteria necessitate the use of different antibiotics leads to non-standardized therapy, although different prescribing practices, drug availability, pathogen frequency and drug resistance in different countries may also be responsible. Ceftriaxone is one of the many antibiotics used for treating this clinical condition in people with SCD and this drug is associated with autoimmune haemolytic anaemia ([Kakaiya 2004](#)). In one observational study including people with SCD treated with ceftriaxone in an emergency department, it was reported that ceftriaxone use may not be justified ([Jain 2002](#)). While prophylaxis with daily oral penicillin is effective in reducing both the rate of infection and the mortality related to pneumococcal infection ([Davies 2004](#); [Gaston 1986](#)), this is not the sole cause of CAP. Furthermore, compliance with oral penicillin is unfortunately not always optimal and this may contribute to rising incidence of penicillin-resistant pneumococci in the community ([Arason 1996](#)). Despite the use of penicillin prophylaxis and pneumococcal polysaccharide vaccines, rates of invasive pneumococcal infection have continued to be observed (three out of 100) in some groups of children with SCD ([Overturf 1999](#); [Overturf 2000](#)). In a systematic review of non-randomised

evidence that included cases with and controls without invasive bacterial disease, the odds of SCD was 19-times greater among cases than controls (Ramakrishnan 2010). For disease caused by *Streptococcus pneumoniae*, the odds of SCD was 36-times greater (Ramakrishnan 2010); and for *Haemophilus influenzae* type b disease it was 13-times greater (Ramakrishnan 2010).

How the intervention might work

β -lactam antibiotics (penicillins, amino-penicillins, cephalosporins) are the drugs for treating CAP in people with SCD, and they inhibit the synthesis of the bacterial peptidoglycan cell wall (Petri 2001).

Why it is important to do this review

This review aims to address the question: which antibiotics (monotherapy or in combination) are most effective for treating people with SCD suffering from CAP?

This is an update of a previously published Cochrane Review (Martí-Carvajal 2006; Martí-Carvajal 2012).

OBJECTIVES

To determine the clinical effectiveness and safety of the antibiotic treatment approaches (monotherapy or combined) for people with sickle cell disease suffering from CAP.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing different antibiotic regimens for CAP in people with SCD, 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) or country.

Types of participants

People with SCD, at any age, with CAP both outpatients (ambulatory) or inpatients (hospitalised), and based in any country.

CAP was defined as an acute infection with a proven infectious agent (from blood, sputum, or by rising antibody levels) of the pulmonary parenchyma that is associated with at least some symptoms of acute infection, accompanied by the presence of an acute infiltrate on a chest radiograph or auscultatory findings consistent with pneumonia (such as altered breath sounds or localized rales or both), in an individual not hospitalized or residing in a long-term care facility for more than 14 days before onset of symptoms (Bartlett 2000).

Types of interventions

We planned to include comparative studies of antibiotics (monotherapy or in combination), administered parenterally or orally and compared with another antibiotic for treating CAP in people with SCD.

The antibiotics were planned to be classified, with some modification as follows (Selim 2010):

1. penicillins (1st, 2nd, 3rd generation: natural; penicillinase-resistant; aminopenicillins)
2. anti-pseudomonal penicillins (4th generation)
3. cephalosporins (1st and 2nd generation)
4. cephalosporins (3rd and 4th generation)
5. carbapenems
6. aminoglycosides
7. quinolones
8. metronidazole
9. clindamycin
10. vancomycin
11. macrolides
12. others

Types of outcome measures

Primary outcome

1. Mortality
 - a. pneumonia-related mortality (if pneumonia was the underlying or immediate cause of death or played a major role in the cause of death) (Mortensen 2002)
 - b. pneumonia-unrelated mortality
2. Number of days to become afebrile*

*This has been re-classified from a secondary outcome.

Secondary outcomes

1. Onset of pain crisis or complications of SCD following CAP diagnosis
2. Hospitalization
 - a. admission rate
 - b. length of hospital stay
3. Respiratory failure rate
4. Number of participants receiving a blood transfusion

Adverse events

We defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines (ICH-GCP 1997) as any event that leads to death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability, and any important medical event, which might have jeopardised the individual or requires intervention to prevent it. All other adverse events are considered non-serious.

Search methods for identification of studies

Electronic searches

Relevant trials were identified from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register using the terms: sickle cell AND (community acquired pneumonia OR low tract infection- ti/abstr) also sickle cell AND pneumococcal.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is 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](#).

Date of most recent search: 01 September 2016.

We searched the following for relevant trials ([Appendix 2](#); [Appendix 3](#)).

- LILACS (1982 to 01 September 2016)
- African Index Medicus (<http://apps.who.int/trialsearch/AdvSearch.aspx>) (1982 to 20 October 2016)

Searching other resources

We searched the [World Health Organization International Clinical Trials](#) ([Appendix 4](#)). Date of last search: 20 October 2016.

We searched the [ClinicalTrials.gov](#) ([Appendix 5](#)). Date of last search: 20 October 2016.

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

Data collection and analysis

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

Selection of studies

Each review author (Arturo Martí-Carvajal (AMC) and Lucieni Oliveira Conterno (LOC)) will independently assess each reference identified by the searches to see if they met the inclusion criteria. If disagreement arises on the suitability of a trial for inclusion in the review, we plan to reach a consensus by discussion.

Data extraction and management

Each review author (AMC, LOC) will independently extract the data from included trials. If disagreement arises on the assessment of trial quality, we plan to reach a consensus by discussion.

We will use the statistical package RevMan 5.1 provided by the Cochrane Collaboration ([RevMan 2011](#)).

Assessment of risk of bias in included studies

Each review author (AMC, LOC) will independently assess the quality 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 5.1* ([Higgins 2011](#)). We will compare the assessments and discuss any discrepancies between the authors.

We will assess the following domains as low risk of bias, unclear or high risk of bias ([Higgins 2011](#)).

1. Generation of allocation sequence

2. Allocation concealment
3. Blinding (of participants, personnel and outcome assessors)
4. Incomplete outcome data
5. Selective reporting
6. Other sources

1. Generation of allocation sequence (checking for possible selection bias)

We will describe, for each included study, the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear, if the trial was described as randomized, but the method used for the allocation sequence generation was not described.

2. Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear, if the trial was described as randomized, but the method used to conceal the allocation was not described.

3. Blinding or masking (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will judge studies at low risk of bias if they were blinded, or if we will judge that the lack of blinding could not have affected the results. We will assess blinding separately for different outcomes or classes of outcomes. We will assess the methods as:

- low risk, high risk or unclear for participants;
- low risk, high risk or unclear for personnel;
- low risk, high risk or unclear for outcome assessors.

4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We will assess the studies in the following way.

- Low risk (any one of the following): no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not

enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.

- High risk (any one of the following): reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; potentially inappropriate application of simple imputation.
- Unclear risk (any one of the following): insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomized not stated, no reasons for missing data provided); the study did not address this outcome.

5. Selective reporting bias (reporting bias due to selective outcome reporting)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods in the following way.

- Low risk (any one of the following): the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
- High risk (any one of the following): not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. sub scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear: insufficient information to permit judgement of 'low risk' or 'high risk'.

6. Free of other bias (bias due to problems not covered elsewhere in the table)

We will describe for each included study any important concerns we have about other possible sources of bias (baseline imbalance, sponsorship bias, confirmation bias, bias of the presentation data, etc).

- 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.

7. Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the *Cochrane Handbook of Systematic reviews of Interventions* (Higgins 2011). With reference to the first six domains above, we plan to assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. Trials assessed as having 'low risk of bias' in all of the specified above individual domains will be considered 'trials with low risk of bias'.

Trials assessed as having 'unclear risk of bias' or 'high risk of bias' in one or more of the specified above individual domains will be considered trials with a 'high risk of bias'

Measures of treatment effect

We plan to summarise binary outcome measures (mortality, pneumonia-unrelated mortality, onset of pain crisis or complications of SCD following CAP diagnosis, respiratory failure rate, number of participants receiving a blood transfusion, and safety) in terms of risk ratios (RR), with 95% confidence intervals (CIs), by extracting numbers in each group.

For continuous outcomes (number of participants receiving a blood transfusion) we plan to record either mean change from baseline for each group or mean post-treatment or intervention values and their standard deviation (SD) or standard error (SE) for each group. We also plan to calculate a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% CIs. If statistics are missing (such as standard deviations), we will try to extract them from other relevant information in the paper, such as P-values and CIs. If this is not possible, the first author of the paper will be contacted.

For time to event outcomes (number of days to become afebrile, days of hospital stay) we plan to record the log-hazard ratio and standard errors from Cox proportional hazards models then combine study results using the generic inverse variance method. If only log-rank or a mixture of log-rank and Cox model estimates are available, the log rank estimates will first be converted into log-hazard ratios with associated standard errors.

We will examine data to see if there is evidence of a skewed distribution using the means and standard deviations as described in the *Cochrane Handbook of Systematic Reviews for Interventions* (Higgins 2011). Continuous data will be classed as being skewed if the standard deviation is over half the size of the mean (this is only true if the data can take positive values only, it does not apply to change data, for example). If data are skewed, when appropriate, we will aim to present log-transformed data. Skewed data will not be pooled, the results will be presented in additional tables, with no statistical analyses performed on these data.

Dealing with missing data

Additional information will be requested from the primary authors of the included trials, when necessary.

In order to allow an intention-to-treat analysis, we will seek data on the number of participants by allocated 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). We will consider there to be significant statistical heterogeneity if I^2 is over 50% (Higgins 2011).

Assessment of reporting biases

We will attempt to assess whether the review is subject to publication bias by using a funnel plot to graphically illustrate variability between trials. If asymmetry is detected, causes other than publication bias will be explored.

We will attempt to contact subject experts and any other relevant register databases in an attempt to identify unpublished papers. Our aim is to reduce the chance of outcome reporting bias.

Data synthesis

If any future identified trials are comparable, we will summarize their findings using a fixed-effect model, if not (I^2 is over 50%), we will use a random-effects model, and we will investigate the cause of the heterogeneity according to the Cochrane Handbook of Systematic Reviews for Interventions (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

Where heterogeneity is found, the possible causes will be investigated further. If significant heterogeneity is detected, we will investigate possible causes for heterogeneity by conducting one or more of the following subgroup analyses:

1. severity of disease;
2. use of antibiotic covering atypical agents;
3. participants on ventilatory support;
4. participants' age;
5. antibiotics' routes of administration;
6. SS type versus SC type.

Sensitivity analysis

If sufficient trials are identified, we plan to conduct a sensitivity analysis comparing the results using all trials and using only those of high methodological quality (studies classified as having a 'low risk of bias' versus those identified as having a 'high risk of bias') (Higgins 2011).

Summary of findings

We will use the principles of the GRADE system (Guyatt 2011a) to assess the quality of the body of evidence associated with all primary and secondary outcomes (mortality, number of days to become afebrile, onset of pain crisis or complications of SCD following CAP diagnosis, respiratory failure rate, number of participants receiving a blood transfusion, adverse events) using the GRADE profiler software (GRADEPro 2014). 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 the risk of publication bias (Balsheim 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h).

RESULTS

Description of studies

After manually checking the titles and abstracts, none of the references identified were eligible for further evaluation.

Risk of bias in included studies

No RCTs were included.

Effects of interventions

The search did not identify any RCTs 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 or safety of antibiotic treatment approaches for treating community-acquired pneumonia (CAP) 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; CAP can be an emergency in people with SCD (Hampton 2005).

Overall completeness and applicability of evidence

This Cochrane Review did not find randomized controlled trials (RCTs) of antibiotics for treating CAP 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 CAP.

In 2002, WHO recognized a decline in child mortality due to pneumonia, but stated that it remains a very important cause of death in developing countries (WHO 2002). Bacterial infections are still a major cause of morbidity and mortality among young children with SCD (Ashley-Koch 2000; Falcao 1989; Lepage 2004; Pelton 2005; Pimentel 2003). These children have an increased prevalence of single and multiple attacks of pneumonia, which run a more serious clinical course than in those people without SCD (De Ceulaer 1985; Sandora 2005). Several infectious agents can produce pneumonia in people with SCD (Landesman 1982); even with current vaccination and prophylactic antibiotic regimens (Adamkiewicz 2003; Bogaert 2004; Sauntharajah 2005). People with SCD are non-immunocompetent hosts (Begue 2001; Landesman 1982; Plouffe 2004).

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 CAP in people with SCD have yet been conducted. This is despite the strong link between pneumonia and SCD; the high frequency of this disease; and the large number of

trials needed to account for the variation in CAP bacteria and their antibiotic sensitivities or resistances due to geography and differing antibiotic prescription practice (Klugman 2004; Metlay 2004; Paradisi 2000; Pimentel 2003). This lack of trials shows a gap between clinical medicine and clinical investigation.

It is widely known that clinicians make practical decisions, often on the basis of inadequate information; this can lead to a poor response to conventional treatment in people with pneumonia (Tan 2004), whilst having an increased risk for developing resistant pneumococcal infections (File 2004; Jacobs 2004; Segreti 2005). Decisions about treatment should be taken 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 sickle cell disease 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).

Quality of the evidence

RCTs were not found on this clinical entity.

Potential biases in the review process

The main limitation of this Cochrane Review is the paucity of evidence in people with SCD suffering from CAP. Publication bias is an important factor that affects the validity of systematic reviews and can modify the quality of the evidence. However, we did an exhaustive search which included many clinical trial registries, but we were not able to find any registered completed trials that were unpublished. Unfortunately, it was not possible to search the EMBASE database from 2008 to 2009.

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

No randomized controlled trials of antibiotics in people with SCD suffering from CAP were found for inclusion in this review. Therefore, it was not possible to determine the efficacy and safety of the antibiotic treatment approaches (monotherapy or combined) for people with CAP suffering from SCD. Hence, we recommend that until evidence becomes available, clinicians continue to treat individuals on a case by case basis given the diagnosis and treatments available to them.

There are no trials included in the review and we have not identified any relevant trials up to September 2016. We therefore do not plan to update this review until new trials are published.

Implications for research

This systematic review has identified the need for well-designed, adequately-powered randomized controlled trials to assess the benefits and harms of antibiotic treatment approaches

(monotherapy or combined) as a way of improving the survival and decreasing mortality from CAP in people with SCD.

Due to the variability of the clinical practice for treating CAP in this population (inter-countries and intra-country), lack of definition of mild CAP in people with SCD, and the immunocompromised state of those individuals, it is not easy to recommend specific outcomes which should be included into RCTs for this clinical entity. For example, some clinical outcomes are not recommended to be included in RCTs for outpatients with mild CAP (mortality, return to "normal" activities of daily living, microbiological response, chest radiography and admission to the hospital) (Gilbert 2008). On the contrary, end points such as patient-reported outcomes and time-to-response are recommended for this clinical issue (Gilbert 2008). Infectious Diseases Society of America has recommended "Design Features of Future Clinical Trials of Antibacterial Agents for Community-Acquired Pneumonia" (ISDA 2008). However, SCD was not specifically considered in that position paper. CAP has a major impact in people with SCD, more so than in people without that hereditary disease which affects the immune system.

The American Society of Hematology has stated "Due to the complexity of this disease, the numerous side-effects of treatments, and the potential for hospitalization, patients should be closely monitored and have access to specialized care" (ASH 2008). Therefore, it would be desirable, in order to improve the well-being and quality of life of that population, to conduct a workshop about this clinical condition in SCD, so that the rules for performing RCTs are defined. This workshop should include haematologists, experts in infectious diseases and methodologists in RCTs from throughout the world.

The trials regarding this issue should be structured and reported according to the CONSORT statement (www.consort-statement.org) for improving the quality of reporting of efficacy and improved reports of harms in clinical research.

ACKNOWLEDGEMENTS

- For this update
 1. Tracey Remmenington from The Cochrane Cystic Fibrosis and Genetic Disorders Group for her help and editorial advice during preparation of this Cochrane Review.
 2. the Iberoamerican Cochrane Centre, Spain.
- For the previous updates and original Cochrane Review.
 1. The Iberoamerican Cochrane Centre, Spain.
 2. Tracey Remmenington from The Cochrane Cystic Fibrosis and Genetic Disorders Group for her help and editorial advice during preparation of this Cochrane Review.
 3. The Contact Editors, Professor Dame Sally Davies and Dr Ian Hambleton for their useful comments.
 4. Nikki Jahnke from the Cochrane Cystic Fibrosis and Genetic Disorders Group for her help and editorial advice during preparation of this Cochrane Review.
 5. Mr Ivan Solá from Iberoamerican Cochrane Centre for his help during preparation of the protocol of this Cochrane Review.

REFERENCES

Additional references

Adamkiewicz 2003

Adamkiewicz TV, Sarnaik S, Buchanan GR, Iyer RV, Miller ST, Pegelow CH et al. Invasive pneumococcal infections in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination. *Journal of Pediatrics* 2003;**143**(4):438-44.

Arason 1996

Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 1996;**313**(7054):387-91.

ASH 2008

Kaushansky K. Special Needs Plan for Chronic Conditions. http://www.hematology.org/policy/testimony/ASH_Comments_re_Special_Needs_Plan_for_Chronic_Conditions.pdf (accessed November 1st 2008).

Ashley-Koch 2000

Ashley-Koch A, Yang Q, Olney RS. Sickle hemoglobin (HbS) allele and sickle cell disease: a HuGE review. *American Journal of Epidemiology* 2000;**151**(9):839-45.

Ballas 2010

Ballas SK, Lief S, Benjamin LJ, Dampier CD, Heeney MM, Hoppe C et al. Definitions of the phenotypic manifestations of sickle cell disease. *American Journal of Hematology* 2010;**85**(1):6-13.

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. [PMID: 21208779]

Bartlett 2000

Bartlett JG, Dowell SF, Mandell LA, File Jr TM, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clinical Infectious Disease* 2000;**31**(2):347-82.

Battersby 2010

Battersby AJ, Knox-Macaulay HH, Carrol ED. Susceptibility to invasive bacterial infections in children with sickle cell disease. *Pediatric Blood & Cancer* 2010;**55**(3):401-6.

Begue 2001

Begue P, Castello-Herbreteau B. Severe infections in children with sickle cell disease: clinical aspects and prevention [Infections graves chez enfant l' drépanocytaire aspects cliniques et prévention]. *Archives de Pédiatrie* 2001;**8**(Suppl 4):732s-41s.

Beytout 2003

Beytout J, Tournilhac O, Laurichesse H. Asplenia and hyposplenism. *La Presse Médicale* 2003;**32**(28 Suppl):S5-9.

Bogaert 2004

Bogaert D, de Groot R, Hermans PWM. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infectious Disease* 2004;**4**(3):144-54.

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**(2):99-110.

Castagnola 2003

Castagnola E, Fioredda F. Prevention of life-threatening infections due to encapsulated bacteria in children with hyposplenism or asplenia: a brief review of current recommendations for practical purposes. *European Journal of Haematology* 2003;**71**(5):319-26.

Castro 1994

Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, Gillette P, et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. *Blood* 1994;**84**(2):643-9.

Castro 2005

Castro O, Gladwin MT. Pulmonary Hypertension in Sickle Cell Disease: Mechanisms, Diagnosis, and Management. *Hematology/Oncology Clinics of North America* 2005;**19**(5):881-96.

Chalmers 2004

Chalmers I. Well informed uncertainties about the effects of treatments. *BMJ* 2004;**328**(7438):475-6.

Chanet 2004

Chanet V, Lesens O, Laurichesse H, Beytout J. Prevention and infection in adults patients with hyposplenism [Infections chez l'adulte asplénique et prévention]. *Medecine et maladies infectieuses* 2004;**34**(11):493-8.

Davies 2004

Davies EG, Hirst C, Lottenberg R, Dower N. Pneumococcal vaccines for sickle cell disease. *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No: CD003885. [DOI: 10.1002/14651858.CD003885.pub2]

De Ceulaer 1985

De Ceulaer K, McMullen KW, Maude GH, Keatinge R, Serjeant GR. Pneumonia in young children with homozygous sickle cell disease: risk and clinical features. *European Journal of Pediatrics* 1985;**144**(3):255-8.

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.

Di Sabatino 2005

Di Sabatino A, Rosado MM, Ciccocioppo R, Cazzola P, Morera R, Corazza GR et al. Depletion of immunoglobulin M memory B cells is associated with splenic hypofunction in inflammatory bowel disease. *The American Journal of Gastroenterology* 2005;**100**(8):1788-95.

Falcao 1989

Falcao RP, Donadi EA. Infection and immunity in sickle cell disease. *Revista da Associacao Medica Brasileira* 1989;**35**(2):70-4.

File 2004

File TM. Streptococcus pneumoniae and community-acquired pneumonia: A cause for concern. *American Journal of Medicine* 2004;**117**(Suppl 3A):39S-50S.

Fleming 1989

Fleming AF. The presentation, management and prevention of crisis in sickle cell disease in Africa. *Blood Review* 1989;**3**(1):18-28.

Gaston 1986

Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G et al. Prophylaxis with oral penicillin in children with sickle cell anemia. *New England Journal of Medicine* 1986;**314**(25):1593-9.

Gilbert 2008

Gilbert DN. Clinical end points of therapy for patients with mild community-acquired pneumonia. *Clinical Infectious Diseases* 2008;**47**(Suppl 3):140-4.

Golden 1998

Golden C, Styles L, Vichinsky E. Acute chest syndrome and sickle cell disease. *Current Opinion in Hematology* 1998;**5**(2):89-92.

GRADEPro 2014 [Computer program]

GRADE Working Group, McMaster University GRADEpro GDT. Version accessed 09 November 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Guyatt 2011a

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. [PMID: 21839614]

Guyatt 2011b

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. [PMID: 21803546]

Guyatt 2011c

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. [PMID: 21802904]

Guyatt 2011d

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. [PMID: 21802903]

Guyatt 2011e

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. [PMID: 21802902]

Guyatt 2011f

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. [PMID: 21247734]

Guyatt 2011g

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. [PMID: 21195583]

Guyatt 2011h

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. [PMID: 21185693]

Haas 2005

Haas H. Antibiotherapy in children with atypical bacterial infections [Antibiothérapie des infections à bactéries atypiques de l'enfant]. *Archives de pediatrie* 2005;**12**(Suppl 1):S45-8.

Hampton 2005

Hampton R, Balasa V, Allen Bracey SE. Emergencies in patients with inherited hemoglobin disorders—An emergency department perspective. *Clinical Pediatric Emergency Medicine* 2005;**6**(3):138-48.

Hebbel 2004

Hebbel RP, Osarogiagbon R, Kaul D. The endothelial biology of sickle cell disease: inflammation and a chronic vasculopathy. *Microcirculation* 2004;**11**:129-51.

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.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good

clinical practice. www.ich.org/cache/compo/276-254-1.html (accessed 18th May 2006).

ISDA 2008

Infectious Diseases Society of America. Position Paper: Recommended Design Features of Future Clinical Trials of Antibacterial Agents for Community-Acquired Pneumonia. *Clinical Infectious Diseases* 2008;**47**(Suppl 3):249-65.

Jacobs 2004

Jacobs MR. Streptococcus pneumoniae: epidemiology and patterns of resistance. *American Journal of Medicine* 2004;**117**(Suppl 3A):3S-15S.

Jain 2002

Jain S, Sullivan K. Ceftriaxone use in the emergency department: are we doing it right? *Pediatric Emergency Care* 2002;**18**:259-64.

Kakaiya 2004

Kakaiya R, Cseri J, Smith S, Silberman S, Rubinas TC, Hoffstadter A. A case of acute hemolysis after ceftriaxone: immune complex mechanism demonstrated by flow cytometry. *Archives of Pathology and Laboratory Medicine* 2004;**128**:905-7.

Klugman 2004

Klugman KP, Low DE, Metlay J, Pechere JC, Weiss K. Community-acquired pneumonia: new management strategies for evolving pathogens and antimicrobial susceptibilities. *International Journal of Antimicrobial Agents* 2004;**24**(5):411-22.

Knight 1999

Knight J, Murphy TM, Browning I. The lung in sickle cell disease. *Pediatric Pulmonology* 1999;**28**(3):205-16.

Landesman 1982

Landesman SH, Rao SP, Ahonkhai VI. Infections in children with sickle cell anemia. Special reference to pneumococcal and salmonella infections. *The American Journal of Pediatric Hematology/Oncology* 1982;**4**(4):407-18.

Lane 1995

Lane PA, O'Connell JL, Lear JL, Rogers ZR, Woods GM, Hassell KL et al. Functional asplenia in hemoglobin SC disease. *Blood* 1995;**85**(8):2238-44.

Lepage 2004

Lepage P, Dresse MF, Forget P, Schmitz V, Hoyoux C. Infections and antibiotic prophylaxis in sickle cell disease. *Revue Medicale de Liege* 2004;**59**(3):145-48.

Lottenberg 2005

Lottenberg R, Hassell KL. An evidence-based approach to the treatment of adults with sickle cell disease. In: Hematology (Am Soc Hematol Educ Program). The American Society of Hematology, 2005.

Loureiro 2005

Loureiro MM, Rozenfeld S. Epidemiology of sickle cell disease hospital admissions in Brazil. *Revista de Saúde Pública* 2005;**39**(6):943-9.

Machado 2005

Machado RF, Gladwin MT. Chronic sickle cell lung disease: new insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension. *British Journal of Hematology* 2005;**129**(4):449-64.

Maitre 2011

Maitre B, Mekontso-Dessap A, Habibi A, Bachir D, Parent F, Godeau B et al. Pulmonary complications in adult sickle cell disease [Complications pulmonaires des syndromes drepanocytaires majeurs chez l'adulte.]. *Revue des Maladies Respiratoires* 2011;**28**(2):129-37.

Makani 2007

Makani J, Williams TN, Marsh K. Sickle cell disease in Africa: burden and research priorities. *Annals of tropical medicine and parasitology* 2007;**101**(1):3-14. [PMID: 17244405]

Makani 2011

Makani J, Cox SE, Soka D, Komba AN, Oruo J, Mwamtemi H et al. Mortality in sickle cell anemia in Africa: a prospective cohort study in Tanzania. *PloS one* 2011;**6**(2):e14699.

Melles 2004

Melles DC, de Marie S. Prevention of infections in hyposplenic and asplenic patients: an update. *The Netherlands Journal of Medicine* 2004;**62**(2):45-52.

Metlay 2004

Metlay JP. Antibacterial drug resistance: implications for the treatment of patients with community-acquired pneumonia. *Infectious disease clinics of North America* 2004;**18**(4):777-90.

Miller 2007

Miller ML, Gao G, Pestina T, Persons D, Tuomanen E. Hypersusceptibility to invasive pneumococcal infection in experimental sickle cell disease involves platelet-activating factor receptor. *Journal of Infectious Disease* 2007;**195**:581-4. [MEDLINE: 17230418]

Modell 2008

Modell B, Darlison M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization* 2008;**86**(6):480-7.

Mortensen 2002

Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Archives of Internal Medicine* 2002;**162**(9):1059-64.

Mousa 2010

Mousa SA, Qari MH. Diagnosis and management of sickle cell disorders. *Methods in Molecular Biology* 2010;**663**:291-307.

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.

NIH 2002

National Heart, Lung, and Blood Institute, Division of Blood Disease and Resources. The Management of Sickle Cell Disease. 4th edition. National Institutes of Health, 2002.

Orkin 2010

Orkin SH, Higgs DR. Medicine. Sickle cell disease at 100 years. *Science* 2010;**329**(5989):291-2.

Overturf 1999

Overturf GD. Infections and immunizations of children with sickle cell disease. *Advances in Pediatric Infectious Diseases* 1999;**14**:191-218.

Overturf 2000

Overturf GD. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. *Pediatrics* 2000;**106**(2 Pt 1):367-76.

Paradisi 2000

Paradisi F, Corti G. Antibiotic resistance in community-acquired pulmonary pathogens. *Seminars in Respiratory and Critical Care Medicine* 2000;**21**(1):33-43.

Pauling 1949

Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. *Science* 1949;**110**(2865):543-6.

Pelton 2005

Pelton SI, Hammerschlag MR. Overcoming current obstacles in the management of bacterial community-acquired pneumonia in ambulatory children. *Clinical Pediatrics* 2005;**44**(1):1-17.

Petri 2001

Petri Jr WA. Penicillins, cephalosporins, and other β -lactam antibiotics. In: Hardman JG, Limbird LE, editors(s). Goodman & Gilman's. The Pharmacological Basis of Therapeutics. 10 edition. New York: McGraw Hill, 2001:1189-218.

Pimentel 2003

Pimentel L, McPherson SJ. Community-acquired pneumonia in the emergency department: a practical approach to diagnosis and management. *Emergency Medicine Clinics of North America* 2003;**21**(2):395-420.

Plouffe 2004

Plouffe Jr JF, Martin DR. Re-evaluation of the therapy of severe pneumonia caused by *Streptococcus pneumoniae*. *Infectious Disease Clinics of North America* 2004;**18**(4):963-74.

Prabhakar 2010

Prabhakar H, Haywood C Jr, Molokie R. Sickle cell disease in the United States: looking back and forward at 100 years of progress in management and survival. *American Journal of Hematology* 2010;**85**(5):346-53.

Ramakrishnan 2010

Ramakrishnan M, Moisi JC, Klugman KP, Iglesias JM, Grant LR, Mpoudi-Etame M et al. Increased risk of invasive bacterial

infections in African people with sickle-cell disease: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2010;**10**(5):329-37.

Rees 2010

Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010;**376**(9757):2018-31.

RevMan 2011 [Computer program]

The Cochrane Collaboration Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2011.

Sandora 2005

Sandora TJ, Harper MB. Pneumonia in hospitalized children. *Pediatric Clinics of North America* 2005;**52**(4):1059-81.

Sauntharajah 2005

Sauntharajah Y, Vichinsky EP, Embury SH. Sickle cell disease. In: Hematology: Basic Principles and Practice. Churchill Livingstone, 2005.

Segreti 2005

Segreti J, House HR, Siegel RE. Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. *American Journal of Medicine* 2005;**118**(Suppl 7A):21S-8S.

Selim 2010

Selim AG, Balalis G, Bhaskar B, van Driel ML. Antibiotics for ventilator-associated pneumonia. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No: CD004267. [DOI: [10.1002/14651858.CD004267.pub3](https://doi.org/10.1002/14651858.CD004267.pub3)]

Serjeant 2010

Serjeant GR. One hundred years of sickle cell disease. *British Journal of Haematology* 2010;**151**(5):425-9.

Siddiqui 2003

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

Steinberg 2009

Steinberg MH. Genetic etiologies for phenotypic diversity in sickle cell anemia. *TheScientificWorldJournal* 2009;**9**:46-67. [PMID: 19151898]

Stuart 2001

Stuart MJ, Setty BN. Acute chest syndrome of sickle cell disease: new light on an old problem. *Current Opinion Hematology* 2001;**8**(2):111-22.

Stuart 2004

Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet* 2004;**364**(9442):1343-60.

Tan 2004

Tan JS. Nonresponses and treatment failures with conventional empiric regimens in patients with community-acquired pneumonia. *Infectious Disease Clinics of North America* 2004;**18**(4):883-97.

Vichinsky 1997

Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood* 1997;**89**(5):1787-92.

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**(25):1855-65.

Vij 2010

Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. *Chest* 2010;**138**(4):973-83.

Waghorn 2001

Waghorn DJ. Overwhelming infection in asplenic patients: current best practice preventive measures are not being followed. *Journal Clinical of Pathology* 2001;**54**(3):214-8.

Waterer 2005

Waterer GW, Wunderink RG. Genetic susceptibility to pneumonia. *Clinics in chest medicine* 2005;**26**(1):29-38.

Weatherall 2006

Weatherall D, Akinyanju O, Fucharoen S, Olivieri N, Musgrove P. Inherited Disorders of Hemoglobin. In: Disease Control Priorities in Developing Countries. Vol. **2nd edition**. Washington DC: The World Bank and Oxford University Press, 2006.

WHO 2002

World Health Organization. Evidence base for the community management of pneumonia. [http://www.who.int/child-](http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO_FCH_CAH_02.23.pdf)

[adolescent-health/New_Publications/CHILD_HEALTH/WHO_FCH_CAH_02.23.pdf](http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO_FCH_CAH_02.23.pdf) (accessed 29 December 2005).

WHO 2004

WHO 2004. Pneumococcal vaccines. <http://www.who.int/vaccines/en/pneumococcus.shtml> (accessed 04 February 2005).

WHO 2005

World Health Organization. Monogenic diseases. <http://www.who.int/genomics/public/geneticdiseases/en/index2.html#SCA> (accessed 29 December 2005).

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**(8):1506-28.

Zago 1983

Zago MA, Bottura C. Splenic function in sickle-cell diseases. *Clinical Science (London, England : 1979)* 1983;**65**(3):297-302.

References to other published versions of this review

Martí-Carvajal 2006

Martí-Carvajal AJ, Conterno L. Antibiotics for treating community acquired pneumonia in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No: CD005598. [DOI: [10.1002/14651858.CD005598.pub2](https://doi.org/10.1002/14651858.CD005598.pub2)]

Martí-Carvajal 2012

Martí-Carvajal AJ, Conterno LO. Antibiotics for treating community acquired pneumonia in people with sickle cell disease. *Cochrane Database of Systematic Reviews* 2012, Issue 10. Art. No: CD005598. [DOI: [10.1002/14651858.CD005598.pub3](https://doi.org/10.1002/14651858.CD005598.pub3)]

APPENDICES

Appendix 1. 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 (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 (www.ncbi.nlm.nih.gov/mesh).
Community-acquired Infections	Any infection acquired in the community, that is, contrasted with those acquired in a health care facility (CROSS INFECTION). An infection would be classified as community-acquired if the patient had not recently been in a health	MeSH (Medical Subject Headings). National Library of Medicine (www.ncbi.nlm.nih.gov/mesh).

(Continued)

	care facility or been in contact with someone who had been recently in a health care facility.	
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 (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 (www.ncbi.nlm.nih.gov/mesh).
Pneumonia	Inflammation of any part, segment or lobe, of the lung parenchyma.	MeSH (Medical Subject Headings). National Library of Medicine (www.ncbi.nlm.nih.gov/mesh).
Pneumonia, pneumococcal	A febrile disease caused by <i>Streptococcus pneumoniae</i> .	MeSH (Medical Subject Headings). National Library of Medicine (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 (www.ncbi.nlm.nih.gov/mesh).
Vaccines	Suspensions of killed or attenuated microorganisms (bacteria, viruses, fungi, protozoa, or rickettsiae), antigenic proteins derived from them, or synthetic constructs, administered for the prevention, amelioration, or treatment of infectious and other diseases.	MeSH (Medical Subject Headings). National Library of Medicine (www.ncbi.nlm.nih.gov/mesh).

Appendix 2. Search strategy LILACS - (via www.bireme.br) 1982 to 01/09/2016

Search Strategy

LILACS

Search carried out: 01/09/2016

Searched for all years using advanced search form:

<http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=A>

LINE 1

(sickle or anemia falciforme anemia de celulas falciformes or drepanocytosis or "SICKLE" or "SICKLE CELL HEMOGLOBIN C DISEASE" or "SICKLE CELL HEMOGLOBIN C DISEASE/" or "SICKLE CELL HEMOGLOBIN C DISEASE/BL" or "SICKLE CELL HEMOGLOBIN C DISEASE/CO" or "SICKLE CELL HEMOGLOBIN C DISEASE/DI" or "SICKLE CELL HEMOGLOBIN C DISEASE/DT" or "SICKLE CELL HEMOGLOBIN C DISEASE/EP" or "SICKLE CELL HEMOGLOBIN C DISEASE/ET" or "SICKLE CELL HEMOGLOBIN C DISEASE/GE" or "SICKLE CELL HEMOGLOBIN C DISEASE/MI" or "SICKLE CELL HEMOGLOBIN C DISEASE/PA" or "SICKLE CELL HEMOGLOBIN C DISEASE/PC" or "SICKLE CELL HEMOGLOBIN C DISEASE/PP" or "SICKLE CELL HEMOGLOBIN C DISEASE/TH" or "SICKLE CELL HEMOGLOBIN C DISEASE/UR" or "SICKLECELL" or "ANEMIA, SICKLE CELL" or "ANEMIA, SICKLE CELL/" or "ANEMIA, SICKLE CELL/AN" or "ANEMIA, SICKLE CELL/BL" or "ANEMIA, SICKLE CELL/CL" or "ANEMIA, SICKLE CELL/CN" or "ANEMIA, SICKLE CELL/CO" or "ANEMIA, SICKLE CELL/DI" or "ANEMIA, SICKLE CELL/DT" or "ANEMIA, SICKLE CELL/EH" or "ANEMIA, SICKLE CELL/EN" or "ANEMIA, SICKLE CELL/EP" or "ANEMIA, SICKLE CELL/ET" or "ANEMIA, SICKLE CELL/GE" or "ANEMIA, SICKLE CELL/HI" or "ANEMIA, SICKLE CELL/IM" or "ANEMIA, SICKLE CELL/ME" or "ANEMIA, SICKLE CELL/MI" or "ANEMIA, SICKLE CELL/MO" or "ANEMIA, SICKLE CELL/NU" or "ANEMIA, SICKLE CELL/PA" or "ANEMIA, SICKLE CELL/PC" or "ANEMIA, SICKLE CELL/PP" or "ANEMIA, SICKLE CELL/PX" or "ANEMIA, SICKLE CELL/RI" or "ANEMIA, SICKLE CELL/SU" or "ANEMIA, SICKLE CELL/TH" or "ANEMIA, SICKLE CELL/UR" or "ANEMIA, SICKLE CELL/US" or "HEMOGLOBIN S DISEASE" or "HE-

(Continued)

MOGLOBIN S DISEASE/" or "HEMOGLOBIN S DISEASE/AN" or "HEMOGLOBIN S DISEASE/BL" or "HEMOGLOBIN S DISEASE/CL" or "HEMOGLOBIN S DISEASE/CN" or "HEMOGLOBIN S DISEASE/CO" or "HEMOGLOBIN S DISEASE/DI" or "HEMOGLOBIN S DISEASE/DT" or "HEMOGLOBIN S DISEASE/EH" or "HEMOGLOBIN S DISEASE/EN" or "HEMOGLOBIN S DISEASE/EP" or "HEMOGLOBIN S DISEASE/ET" or "HEMOGLOBIN S DISEASE/GE" or "HEMOGLOBIN S DISEASE/HI" or "HEMOGLOBIN S DISEASE/IM" or "HEMOGLOBIN S DISEASE/ME" or "HEMOGLOBIN S DISEASE/MI" or "HEMOGLOBIN S DISEASE/MO" or "HEMOGLOBIN S DISEASE/NU" or "HEMOGLOBIN S DISEASE/PA" or "HEMOGLOBIN S DISEASE/PC" or "HEMOGLOBIN S DISEASE/PP" or "HEMOGLOBIN S DISEASE/PX" or "HEMOGLOBIN S DISEASE/RI" or "HEMOGLOBIN S DISEASE/SU" or "HEMOGLOBIN S DISEASE/TH" or "HEMOGLOBIN S DISEASE/UR" or "HEMOGLOBIN S DISEASE/US" or "HEMOGLOBIN SC DISEASE" or "HEMOGLOBIN SC DISEASE/" or "HEMOGLOBIN SC DISEASE/BL" or "HEMOGLOBIN SC DISEASE/CO" or "HEMOGLOBIN SC DISEASE/DI" or "HEMOGLOBIN SC DISEASE/DT" or "HEMOGLOBIN SC DISEASE/EP" or "HEMOGLOBIN SC DISEASE/ET" or "HEMOGLOBIN SC DISEASE/GE" or "HEMOGLOBIN SC DISEASE/MI" or "HEMOGLOBIN SC DISEASE/PA" or "HEMOGLOBIN SC DISEASE/PC" or "HEMOGLOBIN SC DISEASE/PP" or "HEMOGLOBIN SC DISEASE/TH" or "HEMOGLOBIN SC DISEASE/UR")

LINE 2

(Neumonia or pneumonia or low tract infection) or "NEUMONIA" or "NEUMONIAADQUIRIDA"

Search results: 19 references

Appendix 3. African Index Medicus (up to 20/10/2016)

African Index Medicus

Search carried out: 01/09/2016

Searched for all years using advanced search form:

<http://indexmedicus.afro.who.int/cgi-bin/wxis.exe/iah/>

LINE 1

(sickle or anemia falciforme anemia de células falciformes or drepanocytosis or "SICKLE" or "SICKLE CELL HEMOGLOBIN C DISEASE" or "SICKLE CELL HEMOGLOBIN C DISEASE/" or "SICKLE CELL HEMOGLOBIN C DISEASE/BL" or "SICKLE CELL HEMOGLOBIN C DISEASE/CO" or "SICKLE CELL HEMOGLOBIN C DISEASE/DI" or "SICKLE CELL HEMOGLOBIN C DISEASE/DT" or "SICKLE CELL HEMOGLOBIN C DISEASE/EP" or "SICKLE CELL HEMOGLOBIN C DISEASE/ET" or "SICKLE CELL HEMOGLOBIN C DISEASE/GE" or "SICKLE CELL HEMOGLOBIN C DISEASE/MI" or "SICKLE CELL HEMOGLOBIN C DISEASE/PA" or "SICKLE CELL HEMOGLOBIN C DISEASE/PC" or "SICKLE CELL HEMOGLOBIN C DISEASE/PP" or "SICKLE CELL HEMOGLOBIN C DISEASE/TH" or "SICKLE CELL HEMOGLOBIN C DISEASE/UR" or "SICKLECELL" or "ANEMIA, SICKLE CELL" or "ANEMIA, SICKLE CELL/" or "ANEMIA, SICKLE CELL/AN" or "ANEMIA, SICKLE CELL/BL" or "ANEMIA, SICKLE CELL/CL" or "ANEMIA, SICKLE CELL/CN" or "ANEMIA, SICKLE CELL/CO" or "ANEMIA, SICKLE CELL/DI" or "ANEMIA, SICKLE CELL/DT" or "ANEMIA, SICKLE CELL/EH" or "ANEMIA, SICKLE CELL/EN" or "ANEMIA, SICKLE CELL/EP" or "ANEMIA, SICKLE CELL/ET" or "ANEMIA, SICKLE CELL/GE" or "ANEMIA, SICKLE CELL/HI" or "ANEMIA, SICKLE CELL/IM" or "ANEMIA, SICKLE CELL/ME" or "ANEMIA, SICKLE CELL/MI" or "ANEMIA, SICKLE CELL/MO" or "ANEMIA, SICKLE CELL/NU" or "ANEMIA, SICKLE CELL/PA" or "ANEMIA, SICKLE CELL/PC" or "ANEMIA, SICKLE CELL/PP" or "ANEMIA, SICKLE CELL/PX" or "ANEMIA, SICKLE CELL/RI" or "ANEMIA, SICKLE CELL/SU" or "ANEMIA, SICKLE CELL/TH" or "ANEMIA, SICKLE CELL/UR" or "ANEMIA, SICKLE CELL/US" or "HEMOGLOBIN S DISEASE" or "HEMOGLOBIN S DISEASE/" or "HEMOGLOBIN S DISEASE/AN" or "HEMOGLOBIN S DISEASE/BL" or "HEMOGLOBIN S DISEASE/CL" or "HEMOGLOBIN S DISEASE/CN" or "HEMOGLOBIN S DISEASE/CO" or "HEMOGLOBIN S DISEASE/DI" or "HEMOGLOBIN S DISEASE/DT" or "HEMOGLOBIN S DISEASE/EH" or "HEMOGLOBIN S DISEASE/EN" or "HEMOGLOBIN S DISEASE/EP" or "HEMOGLOBIN S DISEASE/ET" or "HEMOGLOBIN S DISEASE/GE" or "HEMOGLOBIN S DISEASE/HI" or "HEMOGLOBIN S DISEASE/IM" or "HEMOGLOBIN S DISEASE/ME" or "HEMOGLOBIN S DISEASE/MI" or "HEMOGLOBIN S DISEASE/MO" or "HEMOGLOBIN S DISEASE/NU" or "HEMOGLOBIN S DISEASE/PA" or "HEMOGLOBIN S DISEASE/PC" or "HEMOGLOBIN S DISEASE/PP" or "HEMOGLOBIN S DISEASE/PX" or "HEMOGLOBIN S DISEASE/RI" or "HEMOGLOBIN S DISEASE/SU" or "HEMOGLOBIN S DISEASE/TH" or "HEMOGLOBIN S DISEASE/UR" or "HEMOGLOBIN S DISEASE/US" or "HEMOGLOBIN SC DISEASE" or "HEMOGLOBIN SC DISEASE/" or "HEMOGLOBIN SC DISEASE/BL" or "HEMOGLOBIN SC DISEASE/CO" or "HEMOGLOBIN SC DISEASE/DI" or "HEMOGLOBIN SC DISEASE/DT" or "HEMOGLOBIN SC DISEASE/EP" or "HEMOGLOBIN SC DISEASE/ET" or "HEMOGLOBIN SC DISEASE/GE" or "HEMOGLOBIN SC DISEASE/MI" or "HEMOGLOBIN SC DISEASE/PA" or "HEMOGLOBIN SC DISEASE/PC" or "HEMOGLOBIN SC DISEASE/PP" or "HEMOGLOBIN SC DISEASE/TH" or "HEMOGLOBIN SC DISEASE/UR")

LINE 2

(Neumonia or pneumonia or low tract infection) or "NEUMONIA" or "NEUMONIAADQUIRIDA"

Search results: 0 references

Appendix 4. World Health Organization. International Clinical Trials. Registry Platform Search Portal (20/10/2016)

Search carried out: 01/09/2016

Sickle AND pneumonia AND antibiotic

Results: 0 references.

Appendix 5. ClinicalTrials.gov (20/10/2016)

Search carried out: 01/09/2016

Sickle AND pneumonia

Searched for all years using advanced search form:

<https://clinicaltrials.gov/ct2/results?term=%22sickle%22+AND+%22pneumonia%22>

Results: 16 references.

WHAT'S NEW

Date	Event	Description
8 September 2020	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 2006

Review first published: Issue 3, 2006

Date	Event	Description
22 May 2019	Amended	A correction has been made to the plain language summary.
9 November 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis Haemoglobinopathies Trials Register identified one potentially eligible trial, which was discarded as not relevant. The search of the LILACS database identified 19 references, which were also not relevant to the review. No other potentially relevant trials were identified by the remaining searches.
9 November 2016	New citation required but conclusions have not changed	The 'Plain language summary' has been re-formatted. Further minor changes were made throughout the review.
24 January 2013	Amended	Contact details updated.
21 September 2012	Review declared as stable	There are no trials included in the review up to May 2012. We do not plan to update this review until new trials are published, although we will search the Group's Haemoglobinopathies Fibrosis Trials Register on a two-yearly cycle.
6 September 2012	New citation required but conclusions have not changed	<p>Minor changes have been made throughout the review.</p> <p>The plain language summary has been amended. Some minor and major structural and textual changes to the review have been made throughout:</p> <ol style="list-style-type: none"> 1. number of days to become afebrile is now considered as a primary outcome; 2. assessment risk of bias has been update (Higgins 2011); 3. a summary of finding section has been included for the future update.

Date	Event	Description
		4. a glossary of medical terms relating to SCD has been added (Appendix 1).
24 August 2012	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register and additional searching activities did not identify any potentially relevant trials for inclusion in the review.
9 March 2009	New search has been performed	A search of the Group's Trials Register did not identify any references potentially eligible for inclusion in the review.
5 November 2008	Amended	Converted to new review format.
1 May 2007	New search has been performed	None of the trials identified by the searches in 2007 were eligible for inclusion in the review.

CONTRIBUTIONS OF AUTHORS

Arturo Martí-Carvajal drafted the protocol and the review with comments from Lucieni Conterno and has prepared the updates.

Arturo Martí-Carvajal acts as guarantor for the review.

DECLARATIONS OF INTEREST

All authors: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Iberoamerican Cochrane Network, 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.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of outcome measures

In response to the position paper for recommended design features of future clinical trials of antibacterial agents for community-acquired pneumonia ([ISDA 2008](#)), a second primary outcome measure - the number of days to become afebrile - has been added. This change addresses the increasing possibility that trials conducted in many geographical locations are unlikely to have adequate power to examine the original 'all-cause mortality' endpoint. It therefore allows the inclusion of trials assessing interventions for 'mild' or 'moderate' CAP as defined in the position paper. This new primary endpoint would be assessed by 'time-to-event' analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anemia, Sickle Cell [*complications]; Anti-Bacterial Agents [*therapeutic use]; Community-Acquired Infections [drug therapy]; Pneumonia, Bacterial [*drug therapy]

MeSH check words

Humans