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Oral antibiotics versus parenteral antibiotics for severe pneumonia in children (Review)

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Oral antibiotics versus parenteral antibiotics for severe pneumonia in children.
Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD004979.
DOI: 10.1002/14651858.CD004979.pub2.

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[Intervention Review]

Oral antibiotics versus parenteral antibiotics for severe pneumonia in children

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Rojas-Reyes MX, Granados Rugeles C. Oral antibiotics versus parenteral antibiotics for severe pneumonia in children. *Cochrane Database of Systematic Reviews* 2006, Issue 2. Art. No.: CD004979. DOI: 10.1002/14651858.CD004979.pub2.

ABSTRACT

Background

Acute respiratory infection (ARI) is one of the leading causes of morbidity and mortality in children under five years of age in developing countries. When hospitalisation is required, the usual practice includes administering parenteral antibiotics if a bacterial infection is suspected. This has disadvantages as it causes pain and discomfort to the children, which may lead to treatment refusal or reduced compliance. It is also associated with needle-related complications. In some settings this equipment is in short supply or unavailable necessitating transfer of the child, which increases risks and healthcare costs.

Objectives

To determine the equivalence in effectiveness and safety of oral antibiotic compared to parenteral antibiotic therapies in the treatment of severe pneumonia in children between three months and five years of age.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2005, issue 2) which contains the Acute Respiratory Infections Group's specialized register; MEDLINE (January 1966 to July 2005); EMBASE (January 1990 to July 2005) and LILACS (February 2005).

Selection criteria

The review included published or unpublished randomised controlled trials (RCTs) and quasi-RCTs comparing any oral antibiotic therapy with any parenteral antibiotic therapy for the treatment of severe pneumonia in children from three months to five years of age.

Data collection and analysis

The search yielded more than 1300 titles. Only three studies met all criteria for eligibility. One of the identified trials is yet to publish its results. We did not perform a meta-analysis because of clinical heterogeneity of therapies compared in the included trials.

Main results

Campbell 1988 compared oral co-trimoxazole versus intramuscular procaine penicillin followed by oral ampicillin in 134 children. At the seventh day of follow up, treatment failure occurred in 6/66 (9.1%) in the oral co-trimoxazole group and 7/68 (10.2%) in the combined-treatment group. The risk difference was -0.01% (95% confidence interval (CI) -0.11 to 0.09). The APPIS Group 2004 evaluated 1702 patients comparing oral amoxicillin versus intravenous penicillin for two days followed by oral amoxicillin. After 48 hours, treatment failure occurred

in 161/845 (19%) in the amoxicillin group and 167/857 (19%) in the parenteral penicillin group. The risk difference was -0.4% (95% CI -4.2 to 3.3). The authors reported similar recovery in both groups at 5 and 14 days.

Authors' conclusions

Oral therapy appears to be an effective and safe alternative to parenteral antibiotics in hospitalised children with severe pneumonia who do not have any serious signs or symptoms.

PLAIN LANGUAGE SUMMARY

Oral antibiotics appear to be as effective as parenteral antibiotics in the treatment of severe pneumonia in children

Acute respiratory infection (including pneumonia) is one of the leading causes of morbidity and mortality in children under five years of age in developing countries. Antibiotics are needed when a bacterial infection is suspected. When children are hospitalised they often receive injectable antibiotics. This has disadvantages: pain, risk of other infections and cost. There are studies that show that oral antibiotics are effective when children are treated as outpatients. The objective of this review was to determine the effectiveness and safety of oral antibiotics compared to parenteral antibiotics in the treatment of pneumonia in children less than five years old. Oral therapy appears to be an effective and safe alternative to parenteral antibiotics in hospitalised children with severe pneumonia who do not have any serious signs or symptoms. There is currently insufficient evidence to determine the relative benefits and harms of oral antibiotics in children with severe pneumonia if serious signs and symptoms are present or in children with severe pneumonia associated with bacterial confirmation or lobar consolidation on chest X-ray.

BACKGROUND

Description of the condition

Acute respiratory infection (ARI) is one of the leading causes of morbidity and mortality in children under five years of age in developing countries (Garenne 1992; WB 1993). It is estimated that 4.3 million children under the age of five die from ARIs each year. In Colombia, ARI is the most frequent reason to attend an outpatient clinic; the most frequent cause of hospitalisation in children less than five years old; and the second most frequent cause of mortality in this age group, after diarrhoea. Present evidence indicates that bacterial infection plays a far greater role as a cause of pneumonia in children in developing countries than it does in developed countries. Bacterial pathogens have been isolated using lung aspirates in up to 74% of patients with pneumonia in developing countries. The primary pathogenic organisms are *Streptococcus pneumoniae (S. pneumoniae)* and *Haemophilus influenzae (H. influenzae)* (WHO 1991).

Description of the intervention

The ARI control programme was developed by the World Health Organization (WHO) in response to the high mortality rate of this illness. Its principal purpose was to reduce mortality and to support the rational use of antibiotics. The recommendations have also been incorporated into the WHO/UNICEF Integrated Management of Childhood Illness (IMCI) programme. These simple strategies provide advice that children with a cough and normal respiratory rate (having a cough or cold) should not be treated with antibiotics or be hospitalised. Children who have rapid breathing but no chest in-drawing (pneumonia) should receive antibiotics as outpatients. Children who have chest in-drawing, with or without rapid breathing (severe pneumonia), should be hospitalised and treated with parenteral penicillin or parenteral ampicillin every six hours for at least three days. After the child recovers, treatment should be changed to oral ampicillin or amoxicillin or intramuscular procaine penicillin. Treatment should continue for at least five days. If the child does not recover within 48 hours of starting treatment with penicillin or if the child's clinical condition deteriorates, antibiotic treatment should be changed to chloramphenicol every six hours. This strategy has resulted in a reduction of mortality when used in developing countries (WHO 1991).

How the intervention might work

Hospitalisation required for the administration of injectable therapy has several drawbacks. Firstly, the routine use of injectable antibiotics, either intravenously or intramuscularly, is associated with a significant increase in the risk of morbidities such as abscess formation and transmission of HIV, hepatitis or other pathogens associated with the use of contaminated needles. Secondly, in some settings, needles for injection and equipment are in short supply or are periodically unavailable. Thirdly, hospitalisation can substantially increase the cost of health care. Fourthly, children who are referred for admission for injectable therapy may not be able to get to the hospital. Finally and most importantly we must keep in mind the discomfort and pain caused to children when receiving injectable antibiotics. Some treatments require daily intramuscular administration of antibiotics. This exposes children to much pain and to potential complications (for example, sciatic nerve injury, infection or local reactions like swelling and redness). As a consequence, there is a concern that the use of injectable antibiotics may reduce compliance with treatment

Recent studies conducted in outpatients (CSG 2002; MASCOT 2002) have shown that oral antibiotics (amoxicillin, co-trimoxazole) are effective and safe treatments in non-severe pneumonia in children in developing countries. The MASCOT 2002 study found that azithromycin is equally effective as amoxicillin-clavulanate acid or erythromycin estolate in the treatment of community-acquired pneumonia in children between six months and 16 years of age. Clinical success (complete recovery of symptoms) was reported as 94% in the azithromycin group and 96% in the control treatment group. Another RCT (Tsarouhas 1998), conducted in a large urban American paediatric emergency clinic, evaluated 170 outpatient children with a radiographic diagnosis of pneumonia. Patients were randomised to receive amoxicillin 50 mg/kg/day or procaine penicillin G 50,000 IU/kg. Treatment failures were 40% (27/68) in the amoxicillin group and 33% (29/86) in the intramuscular penicillin group (risk difference 7%, 95% CI -8 to 23). The authors concluded that there was no significant difference between oral amoxicillin and intramuscular penicillin in the early treatment of non-severe pneumonia in paediatric outpatients

There is less evidence with regard to the use of oral antibiotics in the treatment of severe pneumonia in hospitalised children. Mulholland (Mulholland 1998) studied 144 malnourished children, younger than five years of age, admitted to the General Hospital in Fajara, Gambia with a clinical or radiographic diagnosis of pneumonia. Children were randomly assigned to receive either oral chloramphenicol or oral trimethoprim and sulfamethoxazole (TMP/SMX or co-trimoxazole). Failures were defined as deterioration or failure to improve; death or evidence of persistent pneumonia at the end of seven days of treatment; or clinical or radiographic evidence of pneumonia at the time of the outpatient review. There was no difference in the outcome between malnourished children with pneumonia who received oral TMP/SMX and those who received oral chloramphenicol. The authors found no difference in the outcome between the groups (risk difference 0%, 95% CI -17 to 16). However, the failure rate was high (36%) and this was probably due to the malnourished status of the patients. In addition, the Mulholland study (Mulholland 1998) has several methodological limitations. It had unclear classification and diagnosis criteria; excluded patients from the analysis after randomisation; and had non-specific outcome measurements.

Why it is important to do this review

Whether oral antibiotic treatment strategies can be used effectively and safely in children with severe pneumonia is still unclear. This review helps to find an answer to this question. If oral antibiotics are shown to be as effective as injectable antibiotics in the treatment of severe pneumonia, substantial improvements in access to appropriate care could be achieved. Children would benefit from less pain and discomfort; the reduced risk of certain adverse treatment events (that is to say, nosocomial infections and iatrogenic complications); and lower treatment costs. This review also contributes to the rational use of antibiotics, with avoidance of antibiotic overuse and appropriate antibiotic prescribing.

OBJECTIVES

Primary objective

To determine the equivalence in effectiveness and safety of oral antibiotic and parenteral antibiotic therapies in the treatment of severe pneumonia in children between three months and five years (59 months) of age.

Secondary objectives

1. To describe the proportion of children with severe pneumonia that fail to recover or clinically deteriorate with oral antibiotic therapy compared to parenteral antibiotic therapy.
2. To describe the relative risk of side effects and deaths with oral antibiotic therapy compared to parenteral antibiotic therapy.
3. To describe the mean time for recovery with oral antibiotic therapy compared to parenteral antibiotic therapy.
4. To describe the mean number of days of hospitalisation with oral antibiotic therapy compared to parenteral antibiotic therapy.
5. To describe the costs associated with oral antibiotic therapy compared to parenteral antibiotic therapy.

METHODS

Criteria for considering studies for this review

Types of studies

This review included published or unpublished randomised controlled trials (RCTs) and quasi-RCTs comparing any oral antibiotic therapy with any parenteral antibiotic therapy for the treatment of severe pneumonia in children from three months to five years of age. We looked for eligible studies reported in any language. We excluded studies where children received treatment within the 15 days before the date of recruitment. We also excluded studies which included patients with a chronic pulmonary disease such as asthma, broncho-pulmonary dysplasia, pulmonary hypertension, chronic or recurrent pulmonary diseases, or patients with other diseases such as immunodeficiencies, metabolic disorders, neurological pathologies affecting pulmonary functions or cardiac problems

Types of participants

Children from three to 59 months of age who were diagnosed as having severe pneumonia as defined by WHO:

1. cough for less than two weeks;
2. rapid breathing (defined as a respiratory rate of more than 50 breaths/min in children three months to 12 months old, and more than 40 breaths/min in children 12 to 59 months of age);
3. lower chest in-drawing;
4. absence of laryngeal stridor, somnolence, lethargy, difficulty in drinking liquids, convulsions or more than three episodes of vomiting per hour.

We also looked for eligible studies that used a different but consistent definition for pneumonia

Types of interventions

Types of antibiotics and the dose or duration of therapy used were not restricted. We included any exclusively oral antibiotic therapy compared with any parenteral antibiotic for treatment of severe pneumonia including combination therapies. We classified studies according to the types of therapies compared: oral versus parenteral, and oral versus combined therapies. We defined as combined therapy the use of parenteral antibiotics at the beginning of the treatment followed by oral antibiotics for several days

Types of outcome measures

Primary outcomes

We included studies that assessed any of the following outcome measurements.

1. Absence or persistence of respiratory signs consistent with severe pneumonia (subcostal in-drawings and rapid breathing).
2. Time for recovery of respiratory symptoms.
3. Death within 14 days of randomisation.

Secondary outcomes

We also reviewed studies reporting the following.

1. Changing antibiotic therapy during follow up due to clinical deterioration.
2. Rate of infectious complications (such as empyema or sepsis).
3. Need for ventilation due to respiratory distress.
4. Side effects of the therapy.
5. Length of hospital stay.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library,* 2005, issue 2) which contains the Acute Respiratory Infections Group's specialized register; MEDLINE (January 1966 to July 2005); EMBASE (January 1990 to July 2005); and LILACS (February 2005). We searched MEDLINE and EMBASE using search strategies designed by the Cochrane Acute Respiratory Infections Group. We used the highly sensitive filter designed for identifying RCTs (Dickersin 1994) for searching MEDLINE, in combination with the following specific terms for searching MEDLINE.

MEDLINE (OVID)
1 exp Pneumonia/
2 pneumonia.mp.
3 or/1-2
4 exp Anti-Bacterial Agents/
5 antibiotic$.mp.
6 or/4-5
7 exp Administration, Oral/
8 exp Infusions, Parenteral/
9 parenteral$.mp.
10 exp Injections/
11 injection$.mp.
12 injectable therapy.mp.
13 exp Infusions, Intravenous/
14 intravenous.mp.
15 intramuscular.mp.
16 or/7-15

We modified the above terms for searching EMBASE and LILACS.

Searching other resources

In addition, we scrutinised clinical practice guideline reference lists to identify further trials. We also checked relevant RCT references for additional studies. There were no language restrictions.

We looked for eligible titles and abstracts in the electronic search results and obtained the full text of articles we identified as potentially eligible. To avoid publication bias, we conducted a per protocol handsearch to identify unpublished studies.

(1) We visited websites (searches conducted June 2005) and asked for information about related trials from the following medical and scientific associations:

- American College of Chest Physician (www.chestnet.org);
- American Medical Association (www.ama.org);
- American Academy of Paediatrics (www.apa.org);
- Sociedad Española de Neumopediatría (www.neumoped.org);
- American Association of Respiratory Care (www.aarc.org);
- American Lung Association (www.lungusa.org);
- American Thoracic Society (www.thoracic.org);
- European Respiratory Society;
- www.clinicaltrials.gov;
- The Canadian Lung Association, respiratory review of ERS and the topical reviews of current respiratory literature;
- The Canadian Society of Respiratory Therapists Journal.

(2) We contacted the following pharmaceutical companies:

- Abbott;
- Roche;
- Wyeth;
- Merck;
- Genfar;
- Bayer;
- GlaxoSmithKline;
- Laboratorios MK.

(3) We searched relevant conference abstracts in:

- European Respiratory Society learning resources (www.ersnet.org/ers/lr/browse/default.aspx);
- BIOSI Cardiff School of Biosciences conference talks (www.cf.ac.uk/biosi/research/lung/conferences/conferences.html);
- The British Association for Lung Research Meeting summaries.

Data collection and analysis

Selection of studies

Both of the review authors (MXR and CG) screened the titles identified by the electronic searches, retrieved all potentially relevant studies in full text and evaluated them for inclusion. The authors independently reviewed all full-text articles in a blinded fashion to decide if they met eligibility criteria. Blinded evaluation consisted of masking the authorship information and publication details by a third person, before the review authors assessed the papers. Authors discussed disagreements in the selection of relevant studies and solved the differences by consensus.

Data extraction and management

Both authors independently performed the data extraction. Per each treatment group, the data collected was as follows:

- demographic characteristics of the population studied (origin, gender, age, severity of illness and any other relevant baseline characteristics);
- randomisation procedures;
- number of patients enrolled;
- number of patients analysed;
- details about therapies (type of antibiotic, doses, frequency of administration and total time treatment given);
- treatment side effects and related reported complications;
- follow up (time of follow up, dropouts);
- outcome measures used;
- methods for outcomes assessment;
- total treatment failures (definition and details of treatment failure);
- number of deaths.

Assessment of risk of bias in included studies

Both review authors performed a methodological quality assessment of the trials that met eligibility criteria, using Guyatt's guidelines (Guyatt 2001). The quality issues considered were: randomisation concealment, blinding evaluation of outcomes and follow up. Information was recorded in a form that had been designed in advance.

Unit of analysis issues

We decided that no statistical analysis should be performed to pool the results due to the significant clinical heterogeneity between the included studies. The results of each study are described in the review. Each trial was individually analysed to determine the relative risk and absolute risk difference between treatments for the predetermined categorical outcomes, based on the intention-to-treat principle. According to the outcomes reported in the included studies, persistence of respiratory signs that were consistent with severe pneumonia, changing antibiotic therapy during follow up due to clinical deterioration and the need for ventilation due to respiratory distress were considered as a treatment failure.

If, in the future, the results of individual studies are sufficiently homogeneous to pool results for any of the outcomes, meta-analysis using a random-effects model will be used. In addition to combining all oral antibiotic and all parenteral antibiotic therapies, antibiotics will be classified as follows: cephalosporins, penicillins, macrolides, aminoglycosides and other. Therapies will be considered as equivalent if the 95% CI of the risk difference for the proportion of treatment failures between groups (oral versus parental) are within -5% to 5%. A subgroup analysis will be conducted according to the category of antibiotic used, when this is feasible.

RESULTS

Description of studies

Results of the search

More than 2000 abstracts and titles were scanned. The search yielded 32 potentially eligible studies. Only three met all criteria for eligibility and 29 were rejected (see 'Characteristics of excluded studies' table). Six studies were not controlled trials, 10 studies included only adult populations, eight studies compared only oral therapies, two studies looked at parenteral therapies only, and three studies were excluded because the population studied did not meet the WHO criteria for severe pneumonia or another consistent definition for severe pneumonia.

Included studies

We classified one clinical trial as ongoing (PIVOT Trial 2004). The authors of this study tested the hypothesis: "The outcome of previously well children with community acquired pneumonia treated with oral or intravenous antibiotic therapy will be no different". According to the study protocol, the trial outcome measurements include: length of hospital stay, time for temperature to settle, time to resolution of clinical signs and risks of morbidity and mortality. An e-mail communication with the author informed us that the study has now finished and is ready for publication. By the time of writing this review the PIVOT trial had not yet been published.

Two studies were included in the analysis (APPIS Group 2004; Campbell 1988). Campbell 1988 was conducted in seven rural villages in Gambia. The trial included children from one month to four years of age with severe pneumonia (as defined by the WHO) who had not received antibiotics in the previous two weeks. Patients were sequentially assigned to receive a five-day course of oral co-trimoxazole or a single intramuscular injection of fortified procaine penicillin followed by five days of oral ampicillin (oral versus combined therapy comparison). A total of 134 children were studied with 66 in the oral group and 68 in the combined group, of which 62% and 55% were males, respectively. The mean age was 22 months, and less than 35% of the study population was under one-year old (well balanced in both groups). Children were treated as outpatients due to the reduced resources available in the hospital of the area. Outcomes were assessed at seven days and 14 days after treatment was started. At seven days, trained field workers performed a blinded evaluation of the following outcomes: improvement of condition, defined as in-drawing cessation; reduction of respiratory rates and reduction of temperature. At a 14-day follow-up visit, unblinded project clinicians evaluated the following outcomes: incomplete recovery and the need for further treatment.

APPIS Group 2004 conducted a multi-centre RCT in hospital settings in Asia, Africa and South America. The study population met the WHO severe pneumonia criteria and had no past history or current symptoms of asthma at the time of enrolment (patients had a negative response to the salbutamol test). A total of 1702 children were randomly assigned to receive oral amoxicillin syrup (45 mg/kg/per day in three doses) or parenteral penicillin G (200,000 IU/kg per day in four doses); 857 children were allocated to the oral group and 845 to the injectable group. Gender and age were well balanced in the two treatment groups: 62% in the oral and 63% in the parenteral group were males, 62% were aged 3 to 11 months of age (infants) and 38% were aged one to five years. The main outcome evaluated was treatment failure due to any of the following: worsening of the respiratory condition, low oxygen saturation, persistence of lower chest in-drawing, serious adverse drug reactions, the need to include another antibiotic or to change the antibiotic due to treatment failure, and death. Treatment failure was assessed at 48 hours, 5 days and 14 days after treatment was started.

Risk of bias in included studies

Campbell 1988 used a quasi-randomised allocation method (sequentially) to assign patients to the treatment groups. Therapies were not masked. The evaluators were blinded at the seventh day of the follow-up visit but clinicians who performed the 14-day evaluation of outcomes were not blinded. Analysis was per protocol, but the data reported in the article also allowed an intention-to-treat analysis. According to our quality assessment guidelines this trial had a high risk of bias.

APPIS Group 2004 used the sealed, opaque envelope method for random assignment to the treatment groups; these were prepared in advance by a co-ordinating centre. The assessment of eligibility was standardised among trial physicians before starting the patient enrolments. Therapies were not masked for ethical reasons and evaluation of outcomes was not blinded. However, to minimise the possibility of bias a third physician confirmed all treatment failures. Rates of loss to follow up were lower than 20% and had a similar distribution in both groups. The analysis was by intention to treat. Authors reserved per protocol analysis for the efficacy assessment. According to our quality assessment guidelines this trial had a low risk of bias.

Effects of interventions

Because of clinical heterogeneity of the therapies compared in the included trials, we did not perform a meta-analysis. Therefore, we have described the results of both studies separately and by outcome of interest.

(1) Assessment of treatment failure

Campbell 1988 reported no significant differences in global treatment failure between the two groups (oral versus combined) at two-weeks follow up.
APPIS Group 2004 found no significant differences in treatment failure between the two groups (oral versus parental) at 48 hours, five days and 14 days follow up. The global treatment failure at 48 hours reported by APPIS Group 2004 in the per protocol analysis was 18% for oral versus 19% for parenteral antibiotics (risk difference 0.2%; 95% CI -3.0 to 3.9).

The individual causes of treatment failure addressed by these study authors were as follows.
(a) Lower chest in-drawing
Campbell 1988 did not report outcomes at 48 hours.
APPIS Group 2004 reported no differences for having lower chest in-drawing at 48 hours between the groups (16% oral versus 16% parenteral).
Seven days after treatment started, Campbell 1988 found differences between the groups in chest in-drawing cessation (66.6% oral versus 60.3% combined; risk difference 6.3%; 95% CI -9.8 to 22.6). APPIS Group 2004 reported no differences between the groups with respect to the persistence of lower chest in-drawing at

five days after treatment started (17% oral versus 17% parenteral; risk difference -0.2%; 95% CI -3.8 to 3.3).
At 14 days follow up, APPIS Group 2004 reported no differences between the groups with respect to cumulative treatment failure due to chest in-drawing (18% oral versus 17% parenteral; risk difference -1%; 95% CI -4.7 to 2.6).

Campbell 1988 did not report differential data for chest in-drawing and other causes of treatment failure at 14 days after beginning treatment. However, the authors reported an outcome variable "outcome same or worse", which was similar for the two groups (7.6% oral versus 7.3% combined; risk difference 0.3%; 95% CI -9 to 9).

(b) Clinical deterioration
APPIS Group 2004 evaluated progression to a very severe disease at 48 hours, five days and 14 days after treatment started. There were no differences between groups in the cumulative proportion of patients that presented a clinical deterioration (1% oral versus 1% parenteral; risk difference 0.4; 95% CI -0.6 to 1.4).
Campbell 1988 did not report disaggregated data for clinical deterioration, however, his study reported data on need for admission to hospital due to a very severe illness (2.9% oral versus 4.5% combined).

(c) Deaths and other adverse events
APPIS Group 2004 reported 30 severe, serious adverse events: 8 in the oral group and 22 in the parenteral group. Only 13 were thought to be associated with the study drugs and treatment was changed or discontinued.
In the APPIS Group 2004 seven patients in the parenteral group died (1%) at 48 hours. At the end of follow up (14 days) the cumulative proportion of deaths in each group was 0.2% oral versus 1% parenteral; risk difference -0.6%; 95% CI -0.1 to 1.3. The authors reported from the multivariable regression analysis that, in infant aged 3 to 11 months, severe tachypnoea and hypoxaemia were associated with high fatality rates.
Campbell 1988 reported one death during the follow-up period that occurred in the combined therapy group but the report did not give additional information regarding this outcome.

(d) Other adverse events
Other serious events reported in the APPIS Group 2004 study were diarrhoea (five), rash (five), allergy to penicillin (two) anaemia and malaria (one) severe malaria (three) and unspecified events (two). Neither study reported other outcomes of interest such as need for mechanical ventilation and rate of infectious complications (empyema or sepsis) in any of the treatment groups.

(2) Other outcome measurements

(a) Side effects

APPIS Group 2004 reported no differences in the proportion of patients that required a change of treatment due to side effects related to the study drugs (2% oral versus 3% parenteral).

(b) Mean time to recovery

These data were not reported by either study.

(c) Mean time of hospitalisation

These data were not reported by either study.

(d) Costs associated with hospitalization

These data were not reported by either study.

DISCUSSION

Summary of main results

The most common practice in treating severe pneumonia has been intravenous penicillin administered for several days. However, this requires specialised healthcare workers to administer injections, which are painful for children and stressful for their parents, and probably costs more than using oral therapy. Currently, the evidence from an exhaustive search suggests that there is no significant difference between oral and parenteral antibiotic therapy in the treatment of severe pneumonia in children less than five years of age. The available evidence supports the hypothesis that oral antibiotic treatment strategies could be used as effectively as parenteral therapies in this particular group of children.

The review authors searched for clinical trials from several sources. We searched for trials in any language and scrutinised bibliographic references of identified studies and clinical practice guidelines for treatment of acute respiratory infections in children. In addition, we visited recognised websites of scientific societies and contacted some pharmaceutical companies for further information. Our findings represent the best available evidence about oral versus parenteral antibiotic therapies in the treatment of severe pneumonia in children.

Several authors have tried to evaluate the effectiveness of different antibiotic therapies in the treatment of severe pneumonia in children. Most of them have addressed the clinical effectiveness of two different regimens of combined therapies or two parenteral therapies. One trial included in this review (Campbell 1988) addressed the issue of clinical success in the treatment of severe pneumonia in children from one month to four years of age with oral versus combined therapy (one dose of injectable antibiotics followed by five days of oral antibiotics). We found only one published trial (APPIS Group 2004) that addressed the effectiveness and safety of oral antibiotics compared to parenteral antibiotics in the first 48 hours of treatment of severe pneumonia in children less than five years of age.

Overall completeness and applicability of evidence

Although the two included studies (APPIS Group 2004; Campbell 1988) compared different antibiotic therapies, both had an exclusively oral treatment arm. Both studies reported no differences between groups with respect to treatment failure at one week after treatment started and also no differences in clinical success at the end of treatment and at follow up (14 days). Since neither trial included children with severe pneumonia and serious signs and symptoms (inability to drink, abnormal sleepiness, central cyanosis and convulsions), we cannot draw any conclusions about the role of oral antibiotics compared to parenteral antibiotics in these circumstances. Similarly, these trials did not assess the effects of oral antibiotics in severe pneumonia associated with bacterial confirmation or lobar consolidation identified on chest X-ray.

The studies reviewed did not permit assessment of other important issues relating to the treatment of pneumonia such as, time for recovery of respiratory symptoms and mean number of days of

hospitalisation. This information would assist in the estimation of costs associated with the therapies. The one ongoing trial identified (PIVOT Trial 2004) seems to have measured these outcomes. This trial has been carried out in children admitted to hospital with severe community-acquired pneumonia, in the UK. Despite this, the PIVOT trial results could help to define other outcomes related to time to recovery and length of hospital stay with each type of treatment (oral and parenteral) that can be applied to developing countries. This trial will also contribute to knowledge about clinical treatment failure criteria and morbidity and mortality risks within hospital settings in developed countries. Any future updates of this review will hopefully include the PIVOT trial.

The available evidence supports the hypothesis that oral antibiotic treatment strategies can be used as effectively as parental therapies in this particular instance. These findings have important implications for the treatment of children with severe pneumonia in developing countries; particularly the reduction of needle-associated complications and patient discomfort during treatment.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence from one large well-designed trial supports equivalence in the effectiveness of oral amoxicillin and intravenous penicillin in the treatment of severe pneumonia in children between three months and five years of age. In this study, there was no substantial difference in global treatment failure or safety aspects at 48 hours, 5 days and 14 days. There is currently insufficient evidence to determine the relative benefits and harms of oral antibiotics in children with severe pneumonia if serious signs and symptoms are present or in children with severe pneumonia associated with bacterial confirmation or lobar consolidation on chest X-ray. There is also insufficient evidence to determine whether oral antibiotics are equivalent to parenteral antibiotics in the prevention of rare complications such as, need for mechanical ventilation, progression to empyema or sepsis.

This equivalence of oral and parenteral antibiotics in terms of treatment failure has important clinical implications for the treatment of children with severe pneumonia. Oral antibiotic treatment provides some advantages over parenteral treatment in terms of reducing patient discomfort, needle-associated complications, need for referral or admission from first-level healthcare centres and direct and indirect costs. To apply these findings in general practice, clinicians must take into account that oral antibiotic therapy showed equivalence in children who were under close supervision by health workers, assuring adherence and quick response to complications. However, in hospital settings it may be difficult for clinicians and for parents to accept oral antibiotic therapy even if it has been shown to be equally effective in treating severe pneumonia in children.

Evidence also suggests that there are no differences in effectiveness between oral co-trimoxazole compared to combined therapy (one dose of parenteral penicillin followed by oral ampicillin). However, these results should be applied carefully since they come from a single small study with a high risk of bias.

Implications for research

Research is needed to determine the effectiveness and safety of exclusively oral antibiotic therapies compared to parenteral antibiotic therapies in children with severe pneumonia when serious signs and symptoms are present and in children with severe pneumonia associated with bacterial confirmation or lobar consolidation on chest X-ray. Further studies in other high-risk groups and studies comparing oral antibiotics for severe pneumonia in out-patient settings are also appropriate. Ideally, these studies should use an accurate definition of severe pneumonia and have enough power to identify differences in responses and treatment failures between therapies in infants and older children.

ACKNOWLEDGEMENTS

We would like to thank: Liz Dooley from the Cochrane ARI Group for helping us in all phases of the review process; Ruth Foxlee for helping us to define search strategies and conducting the database searches; Laura Charry-Anzola as our research assistant; and Ivan Solá from the Iberoamerican Cochrane Centre for her advice. We also acknowledge the Iberoamerican Cochrane Centre for its support. Finally, the author wish to thank the following referees for commenting on the draft review: Janet Wale, Claudio Sanguinetti, Jenny Doust, Mark Jones and Peter Morris.

REFERENCES

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

APPIS Group 2004

Methods	Multicentre, randomized, open-label, equivalency study Intention-to-treat analysis for the main outcome Per protocol analysis for efficacy
Participants	N = 1702 n oral (O) = 857 n parenteral (P) = 845 % Male in group O = 62% group P = 63% Children, admitted to tertiary-care centres in eight developing countries in Asia, Africa and South America Inclusion criteria: aged 3 to 59 months WHO defined severe pneumonia Exclusion criteria: asthma, lower chest in-drawing resolved after two courses of inhaled salbutamol Danger signs of more severe disease and very severe pneumonia as defined by WHO
Interventions	Oral: amoxicillin syrup 45 mg/kg per day in three doses Parenteral: intravenous penicillin G crystalline 200.000 IU/kg per day in four doses
Outcomes	Treatment failure up to 48 hours defined as: appearance of danger signs such as inability to drink, abnormal sleepiness, central cyanosis, convulsions Persistence of lower chest in-drawing Serious adverse drug reaction Necessity of other antibiotic or

APPIS Group 2004 *(Continued)*

	Death Follow up: causes of treatment failure were assessed each six hours for the first 48 hours. After discharge were assessed at five and 14 days after treatment was started
Notes	Non-blinded evaluation of outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Campbell 1988

Methods	Multicentre, controlled study Intention-to-treat analysis
Participants	N = 134 n oral (O) = 66 n parenteral+oral (P+O) = 68 % Male in group O = 62 group P+O = 55 Age mean =22 months Children from seven rural villages of The Gambia Inclusion criteria: WHO defined severe pneumonia Exclusion criteria: Inability to take tablets, signs of very severe pneumonia as WHO define
Interventions	Oral: co-trimoxazole, five days course of WHO recommended doses Parenteral+Oral: procaine penicillin (4 mega units) + benzylpenicillin (1 mega unit) one dose, followed by five day course of oral ampicillin - WHO recommended dosages
Outcomes	Treatment failure at week (seven days after treatment was started): persistence of lower chest in-drawing, other respiratory distress signs and temperature Causes of treatment failure at 14th day of follow up: outcome same or worse Incomplete recovery. Requirement for further treatment Follow up and outcomes assessment: 7th day follow up was performed by blinded and previous trained field workers in a home visit 14th day outcome evaluation was performed by unblinded project clinicians at the health care centre
Notes	Pseudo random allocation (sequential) Outcome assessment at day 14 was unblinded

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Eidan 1999	Not a randomised clinical trial
Blokhin 1997	Not a randomised clinical trial Population studied did not meet the "WHO severe pneumonia criteria"
Brambilla 1992	Two parenteral + oral antibiotics regimens compared
Castro 2001	Study in adults
Duke 2002	Two parenteral antibiotics compared
Ehrenkranz 1992	Study in adults
Fedorov 1992	Non-desegregated data for severe pneumonia
Friis 1984	Effectiveness of the same antibiotic was compared in the treatment of two different conditions: bronchiolitis and pneumonia
Fujiki 2003	Study in adults
Galova 1996	Two oral antibiotics compared
Gatzola 1989	Two oral antibiotics compared
Gracheva 1992	Narrative, non-systematic review
Hammerschlag 2000	Study in adults
Hernandez 1996	Study in adults
Higuera 1996	Two oral antibiotics compared
Jibril 1989	Two oral antibiotics compared
Keeley 1996	Population studied did not meet the "WHO severe pneumonia criteria"
Klein 1995	Two oral antibiotics compared
Krumpe 1999	Study in adults
Lode 1999	Study in adults
Mulholland 1995	Two oral antibiotics compared. Study in malnourished children
Numazaki 2000	Narrative/Non systematic review
Portier 1996	Study in adults
Prinsloo 1974	Two oral antibiotics compared
Saiman 2003	Phase II trial study
Sereda 1994	Two oral antibiotics compared. Study in children with acute or chronic bronchopulmonary diseases

Study	Reason for exclusion
Shames 1970	Study in adults
Tatochenko 1999	Narrative, non-systematic review
Tsarouhas 1998	Population studied not meet the "WHO severe pneumonia criteria"

Characteristics of ongoing studies *[ordered by study ID]*

PIVOT Trial 2004

Trial name or title	Multicentre randomised controlled trial of oral versus intravenous treatment for community acquired pneumonia in children (equivalence study)
Methods	
Participants	Children of 6 months to 16 years with community acquired pneumonia admitted to any of 8 city hospitals in Nottingham (UK)
Interventions	Oral amoxycillin: 8 mg/kg/ per day each 8 hours Intravenous benzylpenicillin, 25 mg/kg per day each 6 hours
Outcomes	Time for the temperature to settle Length of stay. Necessity of rescue treatment
Starting date	September 2002
Contact information	Terence Stephenson (Terence.Stephenson@nottingham.ac.uk)
Notes	Study already finished. Waiting for publication

WHAT'S NEW

Date	Event	Description
8 May 2009	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2004
Review first published: Issue 2, 2006

Date	Event	Description
24 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Maria Ximena Rojas (MXR) and Claudia Granados (CG) co-jointly designed the review, set the statement of objectives and designed the criteria for considering studies for this review.
MXR contributed to writing the background (10%), designing the search strategy (80%), and writing the methods of the review (90%).
CG was mainly responsible for writing the background (90%), and was also involved in designing the search strategy (20%) and writing the methods of the review (10%).

DECLARATIONS OF INTEREST

Claudia Granados, author of this review, took part as a site co-investigator in the APPIS Group 2004 trial in Colombia. However, the final analysis and the review writing were done by the contact author María Ximena Rojas. Dr. Granados´s inputs and comments were discussed and agreed with her.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Ampicillin [administration & dosage]; Anti-Bacterial Agents [*administration & dosage]; Injections, Intramuscular; Penicillin G Procaine [administration & dosage]; Pneumonia [*drug therapy]; Randomized Controlled Trials as Topic; Trimethoprim, Sulfamethoxazole Drug Combination [administration & dosage]

MeSH check words

Child, Preschool; Humans; Infant