Antibiotics for acute asthma (Review)

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Antibiotics for acute asthma

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ABSTRACT

Background

Antibiotics are often prescribed to patients who are admitted to hospital with acute asthma. Their exacerbation is often precipitated by a viral upper respiratory infection (URTI), but in some instances antibiotics are prescribed in spite of questionable efficacy. A lack of strong evidence either to support or to refute the use of treatments in acute asthma leaves room for discussion and debate as to how effective antibiotics are in an acute setting. This review assesses what evidence is available.

Objectives

To determine the efficacy of antibiotics prescribed in the treatment of acute asthma.

Search methods

We searched the Cochrane Airways Group Specialised Register to identify randomised controlled trials. In addition, bibliographies were checked and authors and pharmaceutical companies were contacted. The most recent search was carried out in March 2005.

Selection criteria

Only RCTs or quasi RCTs were eligible for inclusion. Studies were included if patients were treated for acute asthma in the ED or its equivalent with antibiotics or placebo. Two reviewers independently assessed articles for potential relevance, final inclusion, and methodological quality.

Data collection and analysis

Two reviewers completed trial quality assessment and data extraction independently.

Main results

From 128 potential studies, we identified two trials for inclusion in the review. Both trials reported numbers of exacerbations and not patient numbers due to re admissions over the course of the trials. The total number of participants in this review was 97, but values were recorded for 115 exacerbations.

An update search conducted in March 2005 did not identify any further studies.

Authors' conclusions

The role of antibiotics in the treatment of acute asthma is difficult to assess from the current literature. Recommendations regarding antibiotic use in acute asthma will remain consensus driven until more research is conducted which includes larger numbers of patients.

PLAIN LANGUAGE SUMMARY

Not enough evidence on whether antibiotics given to people with acute asthma (without evidence of infection) is effective

Patients with acute asthma who require admission to hospital are often treated with antibiotics, in case the underlying cause of the attack is a bacterial infection. This review examines the evidence regarding this therapy and whether it is justified in patients where x-rays and other diagnostic parameters do not indicate a bacterial infection. A limited number of studies were identified by searches conducted and data from them were extracted and analysed. The review concludes that whilst there may be little evidence to support the use of antibiotics in the treatment of acute asthma, more work is required for specific patient subgroups, notably older patients.

BACKGROUND

Asthma is a common chronic disease, defined as a reversible airflow obstruction. Lung function often deteriorates at night and early in the morning and is usually responsive to treatment. However, many asthmatics experience exacerbations where their quality of life, lung function and medication use change dramatically. Exacerbations can result from a variety of airway irritants. However, infection is an important trigger of acute asthma. While most of these infections are thought to be of viral aetiology, antibiotics are often prescribed, especially in General Practice where there is no access to X-ray facilities (Sachs 1995). Patients often develop symptoms suggestive of underlying infection, such as thick and discoloured sputum, fever and chest pain, in association with exacerbations. While many clinicians perceive these to be bacterial in aetiology, it is likely that such symptoms may be a manifestation of the underlying inflammatory process or of viral infection. Viral infections have been shown to be a key trigger of asthma in children, but more difficult to prove in adults. The role of bacterial infections in acute episodes remains unclear. Despite current recommendations to restrict antibiotic treatment in acute asthma (BTS 1997; NAEPP 1997), antibiotics are often prescribed for exacerbations. Treatment for acute asthma in the emergency department would usually include systemic corticosteroids (Rowe 2000a), beta-agonists (Cates 2000), and ipratropium (Plotnick 2000). Additional treatments such as inhaled corticosteroids (Edmonds 2000) and magnesium sulphate (Rowe 2000b) have also been shown to be beneficial.

Since most exacerbations are thought to result from viral upper respiratory tract infections (URTIs) or allergic phenomena, most current guidelines do not recommend the use of antibiotics in the acute phase (BTS 1997; NAEPP 1997). In fact, most would sug-gest that antibiotics be restricted to those patients with clear evidence of pneumonia or those who fail to respond adequately after aggressive treatment with anti-inflammatory medication. However, antibiotics remain a treatment modality outside these confines, especially in general practice (Sachs 1995). Some studies have been conducted in the treatment of asthma with antibiotics in an acute setting (Shapiro 1974; Graham 1982). The treatment of less severe exacerbations of asthma frequently includes antibiotics as shown by some general practice studies (Sachs 1995).

Given the above information, there remains debate regarding the effectiveness of antibiotics in the treatment of acute asthma. There is a discrepancy between recommendations and practice, and this may be due to the lack of quality evidence-based summaries in the literature. While some clinicians may remain adamant that antibiotics are ineffective, there are some important patient subgroups who might benefit from antibiotics (e.g. older asthmatics with COPD and purulent sputum, asthmatic smokers with coexistent COPD). This systematic review examines the evidence for the effectiveness of oral or IV antibiotic treatment in acute asthma. We know of no systematic review of antibiotic treatment in acute asthma that has been published to date.

OBJECTIVES

The objective of this review is to determine the efficacy of antibiotics in the treatment of exacerbations of asthma.

METHODS

Criteria for considering studies for this review

Types of studies

To be considered, reported studies had to be randomised controlled trials (RCT).

Types of participants

Studies including only patients presenting to an emergency department or its equivalent with acute asthma were considered for inclusion in the review. If patients from other settings could be removed easily from the study (for example if stratified randomisation was employed) the data could also be used. We reviewed studies recruiting either children or adult patients, although patient age formed one of the proposed subgroup analyses. We excluded studies examining patients with chest x-rays suggestive of pneumonia. Studies were permitted if they examined in-patients and/or out-patients.

Types of interventions

Patients must have been randomised to receive either antibiotics or placebo/control in the emergency department. Since patients with acute asthma require additional treatments (e.g. systemic and/or inhaled corticosteroids, beta agonists, ipratropium bromide, magnesium, etc.) data for any co-interventions were recorded or requested from the authors when not reported in the studies. Studies using either intravenous or oral antibiotics were considered, and any dose and duration of treatment initiated during the emergency department visit was included.

Types of outcome measures

All patient outcomes were considered, however the primary and secondary outcomes were:
PRIMARY OUTCOME
(1) health care utilization (admission to hospital; length of stay (LOS); relapse).
SECONDARY OUTCOMES
(1) lung function
(2) other clinical outcomes (e.g., vital signs, symptom scores, adverse effects)
(3) laboratory evaluation (sputum bacteriology/white cell count) and
(4) treatment cost.
Attempts were made to contact the primary investigators of included studies to obtain individual patient data.

Search methods for identification of studies

Trials were identified using the Cochrane Airways Group Specialised Register of trials which is derived from systematic searching of electronic databases including CENTRAL, MEDLINE, EMBASE and CINAHL, and hand-searching of respiratory journals and meeting abstracts. Records in the Specialised Register coded as 'asthma' were searched using the following terms:
(acute* or status* or sever* or emerg* or exacerbat* or hospital*) AND (amoxycillin OR erythromycin OR clarithramycin OR clarithromycin OR ampicillin OR tetracyclin* OR doxycyclin* OR oxytetracyclin* OR ciprofloxacin OR tobramycin OR coamoxyclav OR augmentin OR cotrimoxazole OR antibiotic* or antibacterial* or antibacterial* OR penicillin OR septra OR bactrim OR cipro* OR clavulin* OR ceftin*)
The most recent search of the Register was carried out in March 2005.
Additional efforts to locate potential trials included the following:
(1) We reviewed reference lists of all available primary studies and review articles to identify potentially relevant citations.
(2) We made inquiries regarding other published or unpublished trials known or supported by the authors of the primary studies so that these results could be included in this review.
(3) We contacted the scientific advisors of the various pharmaceutical companies that manufacture respiratory antibiotics for any unpublished or interim results on relevant research.
(4) We searched CENTRAL using the following terms: asthma AND antibiotics
(5) Finally, we made personal contact with colleagues, collaborators and other trialists working in the field of asthma to identify potentially relevant studies.

Data collection and analysis

Retrieval of studies
From the title, abstract, or descriptors, two reviewers (VG, TL) independently reviewed the literature searches to identify potentially relevant trials for full review. We conducted searches of bibliographies and texts to identify additional studies by a single reviewer (VG). From the full text, using specific criteria, two reviewers (VG, TL) independently selected trials for inclusion in this review. Inter-rater reliability was measured by using simple agreement and kappa statistics. Disagreement was to be resolved by consensus or third party adjudication (BHR); however, we reached agreement in all cases.

Assessment of study quality
Two reviewers working independently (VG, TL) performed methodological quality assessment by Inter-rater reliability. This was measured using simple agreement and kappa statistics. Both reviewers used two methods of quality assessment.
First, using the Cochrane approach to assessment of allocation concealment, all trials were scored and entered using the following

principles:
- Grade A: Adequate concealment;
- Grade B: Uncertain;
- Grade C: Clearly inadequate concealment.

In addition, each study was assessed using a 0 to 5 scale (Jadad 1996) and summarised as follows:

(1) Was the study described as randomised? (1 = yes; 0 = no)

(2) Was the study described as double-blind? (1 = yes; 0 = no)

(3) Was there a description of withdrawals and dropouts? (1 = yes; 0 = no)

(4) Was the method of randomisation well described and appropriate? (1 = yes; 0 = no)

(5) Was the method of double blinding well described and appropriate? (1 = yes; 0 = no)

(6) Deduct 1 point if methods for randomisation OR blinding were inappropriate.

Data extraction

Two reviewers (VG, TL) extracted data for the trials and entered into the Cochrane Collaboration software program (Review Manager, Version 4.04). Data extracted comprised of absolute and percentage predicted forced expiratory volume (FEV1) or peak expiratory flow rates (PEFR), results from quality of life (QOL) questionnaires and administrative data (length of hospital stay, relapse etc). We asked primary study authors to confirm data extraction and provide additional clarification and information for the review when necessary. In some cases, we required expansion of graphic representations of data from the manuscripts to estimate missing data.

Statistical considerations

All data were entered into Review Manager (version 4.04). For continuous outcomes, we calculated individual statistics as weighted mean differences (WMD) and 95% confidence intervals (CIs) using a random effects model. For dichotomous variables, we calculated individual statistics as odds ratios (OR) and relative risks (RR) with 95% CIs; again, we used a random effects model. There were insufficient results identified for pooling or for sub grouping purposes. A two-sided P value < 0.05 was considered statistically significant.

R E S U L T S

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

The preliminary searches conducted yielded a total of 128 references. From these references, we identified 12 studies as potentially relevant. Two studies met the criteria for this review (Shapiro 1974; Graham 1982) and the other 10 were excluded (See Excluded Studies section). An update search in March 2005 did not identify any further studies.

Graham (Graham 1982) examined amoxycillin in comparison with placebo administered to sixty adults aged between 13 and 82 years of age following admission to hospital with acute exacerbations of asthma between February and December 1979 at St Bartholomew's Hospital, London, UK. Seventy one exacerbations were reported. There were no significant differences reported between the two treatment groups when they entered the trial (mean age for the active treatment group 41.2 years, and mean age of the placebo group was 37.4 years). Entry criteria for the trial were FEV1 on admission as < 1.5 Litres and/or PEFR < 150 l/min. Participants with abnormal chest X-ray were excluded, as were those with a history of penicillin allergy. Amoxycillin was given orally in 500 mg doses three times per day. The outcome measures used were FEV1, PEFR, forced vital capacity (FVC) and number of days for participants to achieve 50% of overall improvement, as assessed by the physician, patient and according to PEFR.

Shapiro (Shapiro 1974) examined the efficacy of hetacillin in comparison with placebo administered to 37 (the results report 44 exacerbations) children aged between 1 and 18 years following admission to hospital with acute asthma. Acute asthma was defined as a lack of response of severe bronchospasm to three subcutaneous Beta-agonist treatments. The treatment groups were similar in terms of age, sex and sample size. Excluded from the trial were those with bacterial disease (in the opinion of the admitting house staff and the consulting infectious diseases service) and those who had recently received antibiotics. Hetacillin was administered intravenously (100 mg per kg/24 hr) with background therapies including aminophylline and oral corticosteroids.

Risk of bias in included studies

The quality of the included trials can be described as adequate. Graham 1982 scored three points on the Jadad scale, and was graded A on the Cochrane allocation concealment scale following discussion with the authors involved. Shapiro 1974 also scored three on the Jadad scale, and was graded B on the allocation concealment scale.

Effects of interventions

Shapiro 1974 enrolled children and Graham 1982 enrolled adults with one adolescent. The data reported in Graham (Graham 1982) was given as medians and as such could not be transferred into Review Manager 4.1. Nevertheless, the data that it did contain provide an indication as to how effective antibiotics are in the treatment of acute asthma and the information contained in that paper merits inclusion in this review.

Graham 1982

Patients in both treatment groups improved significantly over the course of the trial. However, the % predicted FEV1 in the placebo was much higher than that of the group treated with Amoxycillin. Two patients were withdrawn from the control group due to 'slow clinical progress'. Including the results for these participants at the worst end of each variable, and comparing the results for the two groups shows that there was no clinical benefit in prescribing antibiotics.

Shapiro 1974

At the end of this study, 20 patients had received hetacillin and 24 placebo. The courses of both groups in hospital were similar. Airway function improved at similar rates. The mean length of stay in the active treatment group was shorter than that of the placebo group. However, one participant from the control group suffered from a respiratory arrest and was hospitalised for nine days. The instances of infection in both groups was recorded, but it was shown that only 20% of patients had a viral or mycoplasma infection.

DISCUSSION

The relationship between bacterial respiratory infections and asthma is not clear. This is the first systematic review to study the effect of antibiotics versus standard care in the early treatment of acute asthma. Based on the analysis of two studies including 97 participants, there is insufficient evidence to support or refute the use of antibiotics in the treatment of acute asthma. Whilst we searched for in-patient and out-patient studies, we were only able to identify in-patient publications. Patients receiving antibiotics appear to improve at the same rate as patients not receiving antibiotics and subpopulation analyses were not possible.

Studies in children (Shapiro 1974) and adults (Graham 1982) provide no evidence to support the use of antibiotic treatment in patients with uncomplicated acute asthma. No additional benefit was observed in either case from the use of antibiotics. These findings are similar to those from a study, which investigated exacerbations in ambulatory patients with asthma or chronic obstructive pulmonary disease (COPD) from 25 general practices in the Groningen area of the Netherlands (Sachs 1995). One excluded paper (Martin 1997) suggested that, with the exception of sinusitis, there is little evidence to suggest that bacterial respiratory infection triggers asthma.

The findings of this review are based on two trials. Consequently, the study numbers are too small to be conclusive. By virtue of the participants and variable reporting of outcomes, the results of the two studies do not lend themselves to pooling.

There is a possibility of publication and selection bias in this meta-analysis. However, we conducted a comprehensive literature search, with a systematic strategy to avoid bias. We also attempted to find unpublished trials by consulting experts in the field, searching abstracts from recent conferences, and corresponding with the authors of the included studies. The allocation concealment for one study (Graham 1982) was confirmed by correspondence. We feel we have identified the majority of the research available dealing with this issue, but we acknowledge that more of these types of trials may exist.

There is a possibility of study selection bias, however, we employed two independent reviewers when disagreement was present and we feel confident that the reasons for excluding studies are consistent and appropriate (see Excluded Studies). Our search was comprehensive and will be updated.

AUTHORS' CONCLUSIONS

Implications for practice

No clear conclusions can be drawn from this review since the studies were small. Antibiotics do not appear to provide any added benefit over standard therapy, either in children or adults hospitalised for acute asthma in whom there was clinical suspicion of bacterial infection (children) or no abnormal chest X-ray (adults). The cost, side effects and the risk of allergy to antibiotics are factors that should be taken into account when deciding on what therapies are appropriate. Until more research is completed, firm conclusions regarding the efficacy of antibiotic agents cannot be provided.

Implications for research

More research is required for this topic area. In particular, studies with larger sample sizes, and dealing with important subgroups (such as coexisting COPD, chronic asthma as well as elderly patients) are needed. In addition, studies where antibiotic treatment is guided by results from induced sputum examination may also be helpful.

ACKNOWLEDGEMENTS

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Graham VAL, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. *The Lancet* 1982;**1**(8269):418–21.

Shapiro 1974 *{published data only}*
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References to studies excluded from this review

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Black P. The use of macrolides in the treatment of asthma. *European Respiratory Review* 1996;**6**(38):240–3.

Cogo 1994 *{published data only}*
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Kamada 1993 *{published data only}*
Kamada A, Hill M, Ikle D, Brenner M, Szefler S. Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma. *Journal of Allergy & Clinical Immunology* 1993;**91**(4):873–82.

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Martin B, Caruana-Montaldo B, Caig T. Comprehensive management of asthma. *Drugs of Today* 1997;**33**(3):149–60.

Sachs 1995 *{published data only}*
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Spector 1974 *{published data only}*
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Wyser 1997 *{published data only}*
Wyser C, Soler M, Perruchoud AP. New aspects in the treatment of chronic asthma and chronic obstructive lung diseases [Neue Aspekte in der Behandlung des Asthma bronchiale und chronisch obstruktiver Lungenkrankheiten]. *Schweizerische Medizinische Wochenschrift* 1997;**127**(21):885–90.

References to ongoing studies

White 2001 *{published data only}*
Ongoing study Starting date of trial not provided. Contact author for more information.

Additional references

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Rowe 2000a
Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *The Cochrane Database of Systematic Reviews* 2000, Issue 3.[Art. No.: CD002178. DOI: 10.1002/14651858.CD002178]

Rowe 2000b

    Rowe BH, Bretzlaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *The Cochrane Database of Systematic Reviews* 2000, Issue 1.[Art. No.: CD001490. DOI: 10.1002/14651858.CD001490]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Graham 1982

Methods	Double blind randomised control trial conducted over a 10 month period from February to December 1979 involving patients admitted to hospital with acute asthma defined as FEV1 < 1.5l, and PEFR < 150l/min
Participants	60 patients were involved in the study whose results were reported as 71 exacerbations of asthma. Mean age of treatment group was 41.2 (age range 13 to 82) and 37.4 for the placebo group (age range 19 to 77). Patients were excluded whose chest x-rays were indicative of pneumonia as well as those patients who were allergic to penicillin
Interventions	Amoxycillin was given orally in 500mg doses 3 times per day
Outcomes	FEV1, PEFR, FVC and number of days for patients to achieve 50% of overall improvement, as assessed by physician, patient and according to PEFR
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Shapiro 1974

Methods	Double Blind randomised controlled trial over an 11 month period from Septmber 1971 to July 1972 examining patients admitted to hospital with status asthmaticus defined as lack of response to 3 subcutaneous injections of aqueous epinephrine. There was no evidence of bacterial infection and patients had not recently received antibiotics
Participants	37 patients whose results are reported as 44 exacerbations. Mean age of treatment group was 9.3 (SD 4.3) and 7.9 (5.0) in the placebo group. Exclusion criteria were as follows: (1) Bacterial disease causing otitis media (2) Purulent pharyngitis (3) Fever (4) Lobular pulmonary infiltrate in chest x-ray on admission
Interventions	Hetacillin 100 mg per kg per 24 hours IV, or placebo.
Outcomes	FEV1, FVC. Blood gases, Pulmonary Index score, Length of stay
Notes	

Shapiro 1974 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Insufficient information available to determine allocation procedures (Cochrane Grade B)

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

Study	Reason for exclusion
Black 1996	Review article.
Cogo 1994	Trial examined the role of macrolides in the treatment of acute asthma with coexistent infection
Kamada 1993	The patients involved in the trial had chronic asthma
Klajkovic 1998	Clinical audit
Mariotti 1996	Patients were suffering from COPD
Martin 1997	Review article
Sachs 1995	Trial involved patients with COPD in general practice
Spector 1974	The study examined chronic disease
Thom 1996	Letter to a journal
Wyser 1997	Review article

D A T A   A N D   A N A L Y S E S

Comparison 1.   Hetacillin versus Placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 % predicted at 12 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 FEV1 % predicted at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 FVC % predicted at 12 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 FVC % predicted at 24 hours	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Length of stay	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1.   Comparison 1 Hetacillin versus Placebo, Outcome 1 FEV1 % predicted at 12 hours.

Review: Antibiotics for acute asthma

Comparison: 1 Hetacillin versus Placebo

Outcome: 1 FEV1 % predicted at 12 hours

Study or subgroup	Hetacillin N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Shapiro 1974	20	40.6 (23.8)	24	35 (14)		5.60 [-6.24, 17.44]

-10   -5   0   5   10

Favours Placebo   Favours Hetacillin

Analysis 1.2. Comparison 1 Hetacillin versus Placebo, Outcome 2 FEV1 % predicted at 24 hours.

Review: Antibiotics for acute asthma

Comparison: 1 Hetacillin versus Placebo

Outcome: 2 FEV1 % predicted at 24 hours

Study or subgroup	Hetacillin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Shapiro 1974	20	61.6 (25.6)	24	51.8 (18.2)		9.80 [-3.58, 23.18]

```
                                    -10   -5    0    5    10
                                  Favours Placebo   Favours Hetacillin
```

Analysis 1.3. Comparison 1 Hetacillin versus Placebo, Outcome 3 FVC % predicted at 12 hours.

Review: Antibiotics for acute asthma

Comparison: 1 Hetacillin versus Placebo
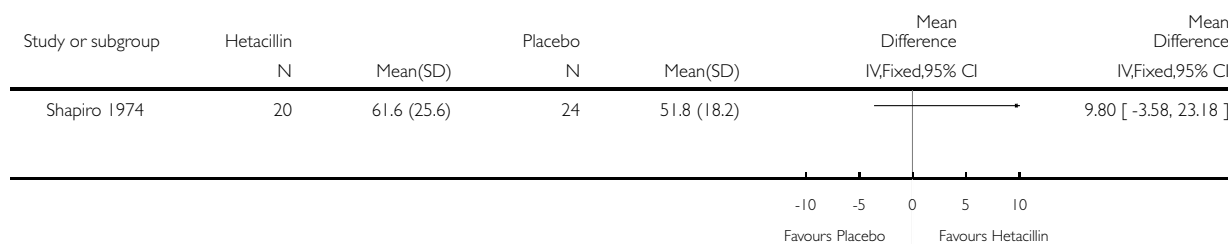
Outcome: 3 FVC % predicted at 12 hours

Study or subgroup	Hetacillin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Shapiro 1974	20	51.8 (28)	24	44.8 (15.4)		7.00 [-6.73, 20.73]

```
                                    -10   -5    0    5    10
                                  Favours Placebo   Favours Hetacillin
```
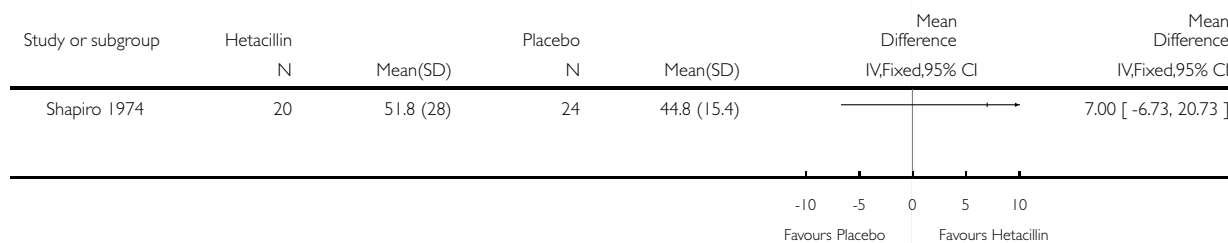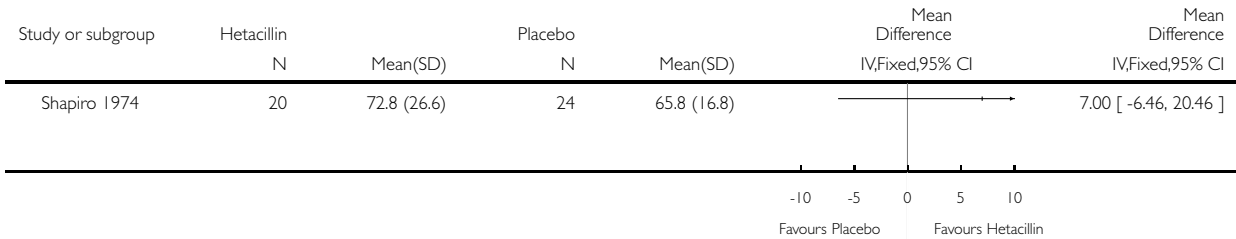
Analysis 1.4. Comparison 1 Hetacillin versus Placebo, Outcome 4 FVC % predicted at 24 hours.

Review: Antibiotics for acute asthma

Comparison: 1 Hetacillin versus Placebo

Outcome: 4 FVC % predicted at 24 hours

Study or subgroup	Hetacillin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Shapiro 1974	20	72.8 (26.6)	24	65.8 (16.8)		7.00 [-6.46, 20.46]

```
        -10   -5    0    5    10
      Favours Placebo    Favours Hetacillin
```
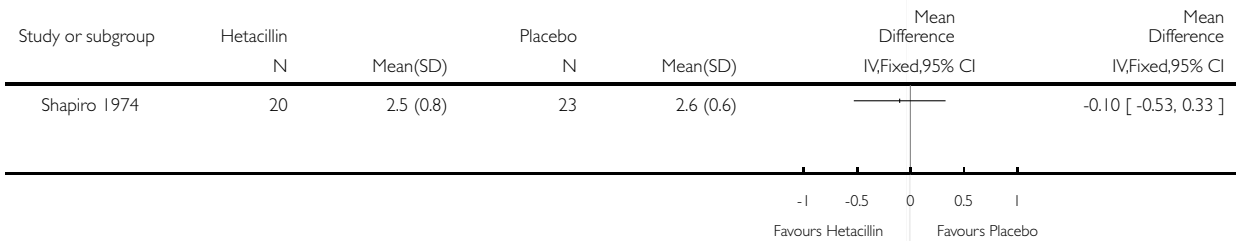
Analysis 1.5. Comparison 1 Hetacillin versus Placebo, Outcome 5 Length of stay.

Review: Antibiotics for acute asthma

Comparison: 1 Hetacillin versus Placebo

Outcome: 5 Length of stay

Study or subgroup	Hetacillin		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Shapiro 1974	20	2.5 (0.8)	23	2.6 (0.6)		-0.10 [-0.53, 0.33]

```
        -1   -0.5    0    0.5    1
      Favours Hetacillin    Favours Placebo
```

WHAT'S NEW

Last assessed as up-to-date: 28 February 2005.

Date	Event	Description
16 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 2, 2001

Date	Event	Description
29 December 2000	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Vanessa Graham: Lead author, protocol development, study selection, quality assessment, data extraction, data analysis, text of review.

Toby Lasserson: protocol development, study selection, quality assessment, data extraction, data analysis, text of review.

Brian Rowe: Protocol development, review write-up and assigned ARG editor.

DECLARATIONS OF INTEREST

The authors who have been involved in this review have done so without any known conflicts of interest. One of the authors was involved with one of the primary studies (Graham 1982). However, none of the authors are considered paid consultants to any pharmaceutical companies that produce antibiotic agents.

SOURCES OF SUPPORT

Internal sources

- Division of Emergency Medicine, University of Alberta, Edmonton, AB, Canada.
- NHS Research and Development, UK.

External sources

- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Age Factors; Anti-Bacterial Agents [*therapeutic use]; Asthma [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans