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Macrolides for diffuse panbronchiolitis (Review)

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[Intervention Review]

Macrolides for diffuse panbronchiolitis

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ABSTRACT

Background

Diffuse panbronchiolitis (DPB) is a chronic airways disease predominantly affecting East Asians. Macrolides, a class of antibiotics, have been used as the main treatment for DPB, based on evidence from retrospective and non-randomised studies.

Objectives

To assess the efficacy and safety of macrolides for DPB.

Search methods

We searched CENTRAL (2014, Issue 6), MEDLINE (1966 to July week 1, 2014), EMBASE (1974 to July 2014), Chinese Biomedical Literature Database (CBM) (1978 to July 2014), China National Knowledge Infrastructure (CNKI) (1974 to July 2014), KoreaMed (1997 to July 2014) and Database of Japana Centra Revuo Medicina (1983 to July 2014).

Selection criteria

Randomised controlled trials (RCTs) or quasi-RCTs assessing the effect of macrolides for DPB.

Data collection and analysis

Two review authors independently assessed study quality and subsequent risk of bias according to The Cochrane Collaboration's tool for assessing risk of bias. The primary outcomes were five-year survival rate, lung function and clinical response. We used risk ratios (RR) for individual trial results in the data analysis and measured all outcomes with 95% confidence intervals (CI).

Main results

Only one RCT (19 participants) with significant methodological limitations was included in this review. It found that the computerised tomography images of all participants treated with a long-term, low-dose macrolide (erythromycin) improved from baseline, while the images of 71.4% of participants in the control group (with no treatment) worsened and 28.6% remained unchanged. Adverse effects were not reported. This review was previously published in 2010 and 2013. For this 2014 update, we identified no new trials for inclusion or exclusion.

Authors' conclusions

There is little evidence for macrolides in the treatment of DPB. We are therefore unable to make any new recommendations. It may be reasonable to use low-dose macrolides soon after diagnosis is made and to continue this treatment for at least six months, according to current guidelines.

PLAIN LANGUAGE SUMMARY

Macrolides for diffuse panbronchiolitis

Research question

To summarise the evidence about the effect and safety of macrolide antibiotics for diffuse panbronchiolitis (DPB).

Background

DPB, characterised by progressive airflow limitation and recurrent respiratory tract infection (RTI), is a chronic airways disease that mainly affects people in east Asia. The prevalence of DPB in Japan is about 11 cases per 100,000 people; the prevalence outside Japan is still unknown.

Macrolides are antibiotics that are used against a wide range of disease-causing bacteria and various infectious diseases. They have been the first choice for DPB since the 1980s, based on several observational studies, which found that they could significantly improve the outcome of DPB. However, high-quality evidence to support their use is unclear.

Study characteristics

We conducted a systematic review of key medical databases, searching for high-quality trials on the use of macrolides in the management of DPB. We retrieved only one randomised controlled trial (RCT) involving 19 participants, which was of poor methodological quality.

Key results

All primary outcomes and most secondary outcomes specified (e.g. five-year survival rate, lung function or clinical response) in our review were not reported in the included trial. The included trial found that the computerised tomography (CT) images of all participants treated with long-term, low-dose erythromycin improved from baseline, while the images of 71.4% of participants with no treatment worsened and 28.6% remained unchanged. Adverse effects were not reported. The evidence is current to July 2014 and we have identified no new trials for inclusion or exclusion.

We conclude that the use of macrolides for DPB is based on non-RCTs or retrospective studies and there is little evidence from RCTs. We are unable to make any new recommendations based on the findings of this review. However, while awaiting evidence from new, high-quality, well-designed studies, it is reasonable to use low-dose macrolides soon after diagnosis is made and to continue for at least six months, according to current guidelines.

Quality of the evidence

We downgraded the quality of the evidence due to limitations in study design, which indicated high risk of potential bias and too small a sample size.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Erythromycin compared with no treatment for diffuse panbronchiolitis

Patient or population: adults with diffuse panbronchiolitis

Settings: outpatient setting

Intervention: erythromycin

Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Erythromycin				
The rate of improvement in CT images (follow-up: 4 to 28 months in the treatment group; 4 to 72 months in the control group)	See comments		RR 15.38 (1.05 to 225.73)	19 (1 study)	⊕⊕⊕⊕ low ^{1,2}	We could not estimate the assumed risk due to lack of relevant studies
The rate of progress in CT images (follow-up: 4 to 28 months in the treatment group; 4 to 72 months in the control group)	See comments		RR 0.06 (0.00 to 0.88)	19 (1 study)	⊕⊕⊕⊕ low ^{1,2}	We could not estimate the assumed risk due to lack of relevant studies

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

¹The study was of small sample size.

²The study was at high risk of bias.

BACKGROUND

Description of the condition

Diffuse panbronchiolitis (DPB), characterised by progressive airflow limitation and recurrent respiratory tract infection (RTI), is a chronic inflammatory lung disease of unknown cause, which predominantly affects East Asians ([Homma 1983](#)). It was first reported in Japan in 1969 by Yamanaka and colleagues ([Yamanaka 1969](#)), and has also been found in other East Asian populations (for example, in China and Korea) ([Chen 2000](#); [Ding 2007](#); [Hu 1996](#); [Izumi 1991](#)). Although case reports and small case series have been described in Western countries, the number of reported cases outside Asia is small and approximately half the cases are among Asian immigrants ([Desai 1989](#); [Fitzgerald 1996](#); [Poletti 1990](#); [Randhawa 1991](#); [Sandrini 2003](#)). According to a survey in 1982, the prevalence of physician-diagnosed DPB in Japan was 11 cases per 100,000 people ([Izumi 1983](#)). However, the prevalence of DPB outside Japan is still unknown.

Over the past two decades, DPB has shifted from being a near-fatal to a treatable disease. A significant improvement in the prognosis of this disease has been attributed to the long-term use of macrolides. Before the use of macrolide therapy, the prognosis of patients with DPB was extremely poor in spite of numerous treatment alternatives, such as other antibiotics, corticosteroids, mucolytic agents (i.e. expectorants) and bronchodilators ([Azuma 2006](#)). The five-year survival rate of DPB patients was 63% in the 1970s, while between 1980 and 1984 it rose to 72%. The five-year survival rate increased to about 90% after treatment with erythromycin became widely used ([Kudoh 1998](#)).

Description of the intervention

Macrolides are broad-spectrum antibiotics, widely used in the treatment of RTIs. Macrolides, including the 14-membered erythromycin, roxithromycin and clarithromycin, the 15-membered azithromycin and the 16-membered josamycin, are active against both gram-positive and gram-negative bacteria, as well as atypical pathogens, such as chlamydia and mycoplasma ([López-Boado 2008](#)). Growing evidence has proven the potent anti-inflammatory and immunomodulatory effects of macrolides when giving a very low dose of the medication, which are significantly lower than a typical antimicrobial dose ([Giamarellos-Bourboulis 2008](#); [López-Boado 2008](#)). Macrolides have been used to treat chronic lung inflammatory diseases, such as DPB, cystic fibrosis, chronic obstructive pulmonary disease, asthma and bronchiectasis ([López-Boado 2008](#)). The possible mechanisms of action of macrolides in the treatment of DPB might include an inhibitory effect on hypersecretion of mucus; an inhibitory effect on the accumulation and proliferation of neutrophils in the mucosa epithelium; and a suppressive effect on lymphocyte activity. However, the antimicrobial effect of macrolides seems not to be related to their beneficial effects on DPB as the treatment dosage is too low to fight against infection ([Giamarellos-Bourboulis 2008](#)).

How the intervention might work

In 1982, Kudoh, of the Tokyo Metropolitan Hospital, first reported a DPB patient treated with erythromycin (600 mg/day) for two years. There was a dramatic improvement in the patient's condition both clinically and radiologically ([Azuma 2006](#)). To confirm this result, an open clinical trial using low-dose erythromycin without a control

group was conducted and the clinical efficacy of erythromycin in patients with DPB was first reported in 1984 ([Kudoh 1984](#)). In 1987, an open trial of low-dose, long-term erythromycin therapy with a four-year follow-up period was reported. After treatment with 600 mg of erythromycin for a period of six months to three years, symptoms and clinical parameters markedly improved in 18 DPB patients. FEV₁ (forced expiratory volume in one second) and PaO₂ (arterial partial pressure of oxygen) were significantly increased ([Kudoh 1987](#)). These favourable effects of erythromycin and other 14-membered ring macrolides, such as clarithromycin and roxithromycin, were soon confirmed by further trials ([Kudoh 1998](#); [Nakamura 1999](#); [Tamaoki 1995](#); [Yamamoto 1990b](#)). Azithromycin, a 15-membered ring macrolide, was seen to have similar effects on DPB ([Kobayashi 1995](#)). Whether or not 16-membered ring macrolides have similar effects has not yet been investigated.

Why it is important to do this review

The Diffuse Lung Disease Committee members of the Ministry of the Health and Welfare of Japan proposed a clinical guideline on macrolide therapy for DPB in 2000, which suggested that macrolides should be started soon after the diagnosis was made and continued for at least six months ([Nakata 2000](#)). However, this recommendation was mainly based on observational studies and expert opinion. As most of these studies were non-randomised or retrospective studies with small sample sizes, the efficacy and safety of macrolides for DPB needs to be evaluated systematically. The aim of this review is to integrate all available randomised controlled trials (RCTs) or quasi-RCTs to provide more reliable evidence for clinicians.

OBJECTIVES

To assess the efficacy and safety of macrolides for DPB.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) or quasi-RCTs.

Types of participants

We included participants of either gender with DPB. DPB was defined by the original trials. We described the diagnostic criteria used by the trial authors in the [Characteristics of included studies](#) table.

Types of interventions

Macrolides, administered for more than two months, versus control interventions (including placebo and other antibiotics).

Types of outcome measures

Primary outcomes

1. Five-year survival rate.
2. Lung function: FEV₁ (forced expiratory volume in one second); FVC (forced vital capacity); TGV (thoracic gas volume); RV/TLC (the ratio of residual volume to total lung capacity) and Gaw (airway conductance).
3. Clinical response: improvement and duration of clinical signs and symptoms.

Secondary outcomes

1. Adverse effects of antibiotic treatment, such as diarrhoea, skin rash and fungal infections.
2. Arterial blood gas (ABG) measurements.
3. Bacterial species in the sputum.
4. Radiological improvement.
5. IL-1, IL-8, TNF- α concentration in bronchoalveolar lavage fluid (BALF).
6. Quality of life.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6) (accessed 16 July 2014), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (2012 to July week 1, 2014), EMBASE (2012 to July 2014), Chinese Biomedical Literature Database (CBM) (2012 to July 2014), China National Knowledge Infrastructure (CNKI) (2012 to July 2014), KoreaMed (2012 to July 2014) and Database of Japana Centra Revuo Medicina (2012 to July 2014). Details of the previous search are in [Appendix 1](#).

We used the search strategy described in [Appendix 2](#) to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format ([Lefebvre 2011](#)). We modified these terms to search the other databases as required. See [Appendix 3](#), [Appendix 4](#), [Appendix 5](#), [Appendix 6](#) and [Appendix 7](#) for individual search strategies for each database.

Searching other resources

We searched for ongoing trials in the following databases in July 2014:

1. ClinicalTrials.gov (<http://clinicaltrials.gov/>);
2. Chinese Clinical Trial Register (www.chictr.org);
3. Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/>);
4. International Standard Randomised Controlled Trial Number (ISRCTN) (<http://www.controlled-trials.com/isrctn/>);
5. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictpr/en/>); and
6. University Hospital Medical Information Network (UMIN) Clinical Trials Registry for Japan (www.umin.ac.jp/ctr/).

We scanned the references of all included trials and relevant reviews to identify other potential trials. One review author (MY) handsearched the *Chinese Journal of Tuberculosis and Respiratory Diseases* (1980 to July 2012), *Chinese Journal of Respiratory and Critical Care Medicine* (1980 to July 2012) and *Chinese Journal of Internal Medicine* (1980 to July 2012). We attempted to contact authors of trials that seemed to meet the inclusion criteria. There were no language or publication restrictions.

For this 2014 update, one review author (XFL) handsearched the *Chinese Journal of Tuberculosis and Respiratory Diseases* (August 2012 to July 2014), the *Chinese Journal of Respiratory and Critical*

Care Medicine (August 2012 to July 2014) and the *Chinese Journal of Internal Medicine* (August 2012 to July 2014).

Data collection and analysis

Selection of studies

Two review authors (in previous versions: MY, JL; for this 2014 update: XFL, JL) independently selected relevant articles and assessed their eligibility according to the inclusion and exclusion criteria, resolving any disagreements by discussion or judgement of the arbiter (in previous versions: BRD; for this 2014 update: MY). Two other review authors (BRD, HMW) were consulted where necessary. We attempted to obtain the full text of the articles identified as either relevant or ambiguous from their titles and abstracts.

Data extraction and management

We used a standardised study record form to extract data, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Two review authors (XFL, MY) independently extracted the data. We resolved discrepancies with an arbiter (BRD). One review author (MY) checked and entered data into RevMan 5.3 for statistical analysis ([RevMan 2014](#)).

Assessment of risk of bias in included studies

Two review authors (XFL, MY) independently assessed the quality of each study and the subsequent risk of bias according to The Cochrane Collaboration's tool for assessing risk of bias ([Higgins 2011](#)). We resolved discrepancies through discussion. If there was insufficient detail about the study method, we tried to contact the trial authors for further information. We wrote letters to the contact author of the trial that met the inclusion criteria, but we received no response, so we assessed risk of bias based on the available information.

We assessed the following items as 'low risk of bias', 'high risk of bias' or 'unclear risk of bias'.

Was there adequate sequence generation?

Low risk of bias: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation (minimisation might be implemented without a random element, and we considered this to be equivalent to being random).

High risk of bias: sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention. We would evaluate quasi-RCTs as 'high risk of bias'.

Unclear: insufficient information about the sequence generation process to permit judgement.

Was allocation adequately concealed?

Low risk of bias: randomisation method described that would not allow the investigator/participant to know or influence the intervention group before an eligible participant entered in the study (for example, central allocation, including telephone, web-based and pharmacy-controlled randomisation; sequentially

numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).

High risk of bias: using an open random allocation schedule (for example, a list of random numbers); assignment envelopes were used without appropriate safeguards (for example, if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure. Allocation schedule was usually impossible to achieve in quasi-RCT. Therefore, we would evaluate this as 'high risk of bias'.

Unclear: randomisation stated but no information on method used is available.

Was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias: blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others was unlikely to introduce bias.

High risk of bias: since some outcomes or outcome measurements, such as improvement in signs and symptoms, were likely to be influenced by lack of blinding, we assessed the following conditions as 'high risk of bias': no blinding or incomplete blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others was likely to introduce bias.

Unclear: insufficient information to permit judgement of 'Yes' or 'No'.

Were incomplete outcome data adequately addressed?

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

High risk of bias: 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 the observed event risk was enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, the plausible effect size (difference in means or standardised difference in means) among missing outcomes was enough to induce clinically relevant bias in the observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Unclear: insufficient information to permit judgement of 'Yes' or 'No'.

Were reports of the study free of suggestion of selective outcome reporting?

Low risk of bias: the study protocol was available and all of the study's pre-specified (primary and secondary) outcomes that were of interest in the review have been reported in the pre-specified way; the study protocol was not available but it was 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 of bias: not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (for example, sub-scales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were 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 'Yes' or 'No'.

Was the study apparently free of other problems that could put it at a risk of bias?

Low risk of bias: the study appears to be free of other sources of bias.

High risk of bias: had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.

Unclear: insufficient information to permit judgement of 'Yes' or 'No'.

Measures of treatment effect

We defined measures of treatment effects according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dichotomous data

We presented dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI) for individual trials. We discussed the findings of each study. Since there was only one RCT included in the review, we could not pool the data.

Continuous data

No continuous data were available in the included RCT.

Ordinal data

There were no ordinal data in the included RCT.

Unit of analysis issues

Individually randomised trials with parallel design

Individual participants were the unit of analysis.

Cluster-randomised trials

There were no cluster-randomised trials that met our inclusion criteria.

Cross-over trials

No cross-over trial was included in this review.

Dealing with missing data

We attempted to contact the trial authors for missing data in order to obtain the necessary information. However, we did not receive any responses. The included RCT reported that there were no drop-outs during the study period, therefore we considered that data were not missed due to drop-out of participants.

Assessment of heterogeneity

As there was only one RCT in this review, assessment of potential heterogeneity was unnecessary.

Assessment of reporting biases

We could not assess reporting biases, since only one RCT was included.

Data synthesis

Data synthesis was not possible.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis could not be done.

Sensitivity analysis

Sensitivity analysis could not be done.

RESULTS

Description of studies

Results of the search

In the previous searches, we identified 327 articles for further assessment. After screening the titles and abstracts, we identified 12 trials as potentially relevant and reviewed the full texts. Of these, trials published in Japanese ([Kudoh 1984](#)) or Korean ([Hyeon 1997](#)) were translated into English. Two review authors (MY, JL) reviewed the full texts. One trial met the inclusion criteria ([Akira 1993](#)). We excluded 11 trials because they were not RCTs ([Kadota 2003](#); [Kadota 2004](#); [Kadota 2005](#); [Hyeon 1997](#); [Kudoh 1984](#); [Kudoh 1998](#); [Nagai 1991](#); [Sato 1993](#); [Shirai 1997](#); [Yamamoto 1990a](#); [Yamamoto 1992](#)).

The updated 2014 search identified an additional 20 potential papers. However, after screening the titles and abstracts, we did not find any new trials for inclusion or exclusion in this review.

Included studies

We identified only one eligible study ([Akira 1993](#)).

Participants

Nineteen adults from 20 to 70 years of age (mean, 50 years) in Japan were included in the study. All participants met the clinical diagnostic criteria for DPB ([Homma 1983](#)). The diagnosis of DPB was also confirmed by transbronchial lung biopsy (n = 12), open lung biopsy (n = 3) or autopsy (n = 4). Participants were randomly allocated into two groups. One group received erythromycin while the other received no treatment. The baseline data for the participants in both groups were not reported. There were no drop-outs during the study period.

Interventions

Twelve participants were randomly assigned to receive long-term, low-dose erythromycin (600 mg/d) and seven were assigned to receive no treatment. The duration of treatment was not clearly described in the report. The trial authors only stated that the participants in the treatment group received erythromycin between the first and second computerised tomography (CT) scan. The interval between the two CT scans ranged from four months to 28 months (mean, 11 months) in the treatment group and from four months to 72 months (mean, 27 months) in the control group.

Outcomes

As we described in the protocol, the primary outcomes for this review were five-year survival rate, lung function (including FEV1, FVC, TGV, RV/TLC and Gaw) or clinical response (for example, improvement in signs and symptoms and the duration of clinical signs and symptoms). However, the included study did not cover any of these issues ([Akira 1993](#)).

Out of our secondary outcomes, only 'improvement of chest radiography' was reported in the study. CT scans were used to evaluate the efficacy of erythromycin for DPB. The images were assessed by two authors of the original study who were blinded to the allocation strategy. DPB in the CT images was classified into four categories:

1. type 1, small nodules around the end of bronchovascular branchings;
2. type 2, small nodules in the centrilobular area of high attenuation;
3. type 3, nodules plus ring-shaped or ductal areas of high attenuation connected to proximal bronchovascular bundles;
4. type 4, large cystic areas of high attenuation plus dilated proximal bronchi.

Type 1 was the mildest, whereas type 4 was the most severe.

The trial did not report details of randomisation, source of funding and ethics approval, details of other treatments given or adverse effects. In addition, our efforts to contact the trial authors for further information were unsuccessful.

Excluded studies

Details of the excluded studies are available in the [Characteristics of excluded studies](#) table. There was a multicentre, prospective, double-blind, placebo-controlled study that seemed to meet our inclusion criteria ([Yamamoto 1992](#)). However, we could not find the method of allocation in the trial report so we could not label it as a RCT. Our efforts to contact the trial authors were unsuccessful.

Risk of bias in included studies

We applied The Cochrane Collaboration's tool for assessing risk of bias. [Figure 1](#) and [Figure 2](#) illustrate the overall risk of bias.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Methods of sequence generation and allocation concealment were not clearly stated in the included study. The risk of bias was therefore unclear.

Blinding

The trial authors did not describe whether the participants were blinded or not. However, they clearly reported that the CT images were appraised by two observers who did not know which participant received erythromycin. The non-blinding of participants was unlikely to introduce bias because the results were objectively assessed by outcome assessors. As a result, we gave a judgement of 'low risk of bias'.

Incomplete outcome data

All randomised participants were included in the analysis, therefore there was a low risk of bias.

Selective reporting

The study protocol was not available and there was not sufficient information to draw a conclusion. The risk of bias was therefore unclear.

Other potential sources of bias

The time to follow-up was different between the treatment group (mean, 11 months) and the control group (mean, 27 months). This may introduce bias. Moreover, the sample size of the study was too small. We therefore gave this a 'high risk of bias'.

Effects of interventions

See: [Summary of findings for the main comparison](#)

The included study only reported the change in CT images in both treatment and control groups (Akira 1993).

Primary outcomes

1. Five-year survival rate

This outcome was not reported in the included trial.

2. Lung function

This outcome was not reported in the included trial.

3. Clinical response: improvement and duration of clinical signs and symptoms

This outcome was not reported in the included trial.

Secondary outcomes

1. Adverse effects of antibiotic treatment

This outcome was not reported in the included trial.

2. Arterial blood gas (ABG) measurements

This outcome was not reported in the included trial.

3. Bacterial species in the sputum

This outcome was not reported in the included trial.

4. Radiological improvement

This outcome was not reported in the included trial.

5. IL-1, IL-8, TNF- α concentration in bronchoalveolar lavage fluid (BALF)

This outcome was not reported in the included trial.

6. Quality of life

This outcome was not reported in the included trial.

Comparison: erythromycin versus no treatment

Changes in computerised tomography (CT) images

In the treatment group, the CT images of all participants improved (i.e. the small rounded centrilobular and branched linear areas of high attenuation decreased in number and size). Two participants improved from type 2 to type 1. However, in the control group, three participants progressed from type 2 to type 3, two participants from type 3 to type 4, and two participants remained unchanged. The rates of improvement in the CT images in the erythromycin group versus no treatment were 100% versus 0% (risk ratio (RR) 15.38, 95% confidence interval (CI) 1.05 to 225.73) (Analysis 1.1; Figure 3). The rates of progress in the CT images in the erythromycin group versus no treatment were 0% versus 71.43% (odds ratio (OR) 0.06, 95% CI 0 to 0.88) (Analysis 1.2; Figure 4).

Figure 3. Forest plot of comparison: 1 Erythromycin versus no treatment, outcome: 1.1 The rate of improvement in CT images.

Figure 4. Forest plot of comparison: 1 Erythromycin versus no treatment, outcome: 1.2 The rate of progress in CT images.

The study did not report any adverse events.

DISCUSSION

Summary of main results

This review identified only one randomised controlled trial (RCT) assessing the effect of macrolides for diffuse panbronchiolitis (DPB) (Akira 1993), which had significant methodological limitations and a small sample size. Moreover, this single study only reported changes in computerised tomography (CT) images before and after treatment with erythromycin. All primary outcomes and most secondary outcomes specified in our review were not covered in the included trial. The study indicated that the CT images of all participants treated with long-term, low-dose erythromycin improved from baseline, while the images of 71.4% of participants in the control group worsened and 28.6% remained unchanged. Adverse events were not reported.

Overall completeness and applicability of evidence

The evidence offered by the included RCT was insufficient (Akira 1993). First of all, as we mentioned above, the trial report did not cover all important clinical endpoints but merely appraised the changes in CT images, which was a typical 'intermediate indicator'. Secondly, only erythromycin was used, whereas the effects of other macrolides, such as clarithromycin and roxithromycin, were not assessed in the study. Furthermore, the safety profiles were not reported in the RCT.

According to the included study, erythromycin was used at a low dosage (600 mg/d) for a long-term period (at least four months, mean 27 months) (Akira 1993). However, the actual duration of the treatment was not described in the report. When applying the evidence to clinical practice, several questions need answers. For example, does the dosage and duration of erythromycin influence the outcome effects or not? Do different kinds of macrolides have distinct effects or not? For what duration should erythromycin be used? What are the indicators to cease treatment with erythromycin? How safe is long-term use of erythromycin? None of these questions have been resolved in this review.

Quality of the evidence

The only included RCT was of poor methodological quality (Akira 1993). Firstly, although it stated that randomisation was used, it did not report the method of randomisation. Secondly, the sample size of the study was too small to permit adequate assessment of this intervention. Finally, the period of follow-up was significantly different between the treatment and control group, which might induce bias.

There are some challenges to conducting a high-quality RCT for DPB. First and most importantly, it is difficult to recruit enough

DPB participants because of low morbidity. Even in Japan, where DPB has the highest incidence, morbidity is only about 11 per 100,000 (Izumi 1983). Secondly, there may be ethical problems if comparing macrolides with placebo or no treatment in new trials, since macrolides have shown an effect in non-RCTs (Kadota 2003; Kadota 2004; Kadota 2005; Hyeon 1997; Shirai 1997; Yamamoto 1992), and are recommended in current guidelines (Nakata 2000).

Potential biases in the review process

Although we tried our best to retrieve all published trials during the course of drafting this review, there might be some missing studies since most potentially relevant studies were conducted and published in Japan. This was the major limitation of our review and may have introduced potential selective reporting bias. Moreover, several articles published in Japanese or Korean were translated into English, and this process might lead to potential bias.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review to evaluate the effect of macrolides for DPB. We searched as many important medical databases as possible, including local medical databases in Japan, China and Korea, as DPB was mainly diagnosed in these countries. After careful assessment, only one RCT was identified (Akira 1993). However, we found several prospective open trials which offer some valuable information on this topic.

Yamamoto conducted a multicentre, double-blind, placebo-controlled trial to evaluate the effects of erythromycin on DPB (Yamamoto 1992). Forty participants were enrolled in the erythromycin group and 45 in the placebo group across 35 medical centres. The erythromycin group was treated with erythromycin (600 mg/d) for three months. It found that the erythromycin group had better outcomes than the placebo group in all of the clinical variables, such as cough, sputum, stridor, dyspnoea on exertion, rales, FEV₁, PaO₂ and C-reactive peptide (CRP). However, these differences had no statistical significance. Compared with the placebo, however, there were significant improvements in chest images and the amount of sputum expectorated during the early morning in the erythromycin group, which were similar to the findings of our review.

A prospective study in Korea enrolled 25 DPB participants who were followed up for more than six months with erythromycin (500 mg/d) and analysed the changes in subjective symptoms, physical signs, pulmonary function tests and chest X-rays (Hyeon 1997). It found that subjective symptoms improved in 96% of the participants within three months and 76% showed no symptoms after 18 months of treatment. Diffuse small nodular lesions on chest X-ray decreased in 56% of patients within three months and chest poster-anterior (PA) film was normal in 32% of the participants after

12 months of treatment. No participants experienced side effects from erythromycin.

Some case reports in China have reported that macrolides (including erythromycin, clarithromycin and roxithromycin) are effective in improving the symptoms and lesions in chest X-ray or CT images (Bai 2000; Chen 2007; Hou 1998; Hu 2009; Li 2007; Liu 1999; Liu 2006; Tan 2006; Xue 2002; Zai 2009). However, we failed to find any clinical trials which focused on this topic in China.

In addition to the prospective trials mentioned above, several observational studies in Japan indicated that macrolides could significantly improve the prognosis of DPB, while causing few side effects (Kudoh 1984; Kudoh 1987; Kudoh 1998; Kobayashi 1995; Nakamura 1999; Tamaoki 1995; Yamamoto 1990b). For this reason, although there was only one RCT to support macrolide use in DPB, the guidelines proposed by the Diffuse Lung Disease Committee members of the Ministry of the Health and Welfare of Japan still recommend macrolides as the first choice for DPB.

AUTHORS' CONCLUSIONS

Implications for practice

This review highlights the absence of high-quality evidence to support the use of macrolides in the treatment of diffuse panbronchiolitis (DPB). We are therefore unable to make any new recommendations based on the findings of this review. The poorly reported single randomised controlled trial (RCT) included in this review shows that long-term, low-dose erythromycin (600 mg/d, for at least four months) significantly improves radiological changes in DPB patients. While awaiting new evidence from well-

designed studies, macrolides should still be used soon after the diagnosis is made and continued for at least six months, according to current guidelines (Nakata 2000).

Implications for research

Given the routine use of macrolides in the management of DPB and the low morbidity associated with DPB, there is a need for academic debate about the ethics and practicality of randomised trials in order to define the true extent of benefits. In particular, more information is required on the subset of patients who are more likely to benefit from this therapy and the most appropriate type, dose and duration of administration. Since it may be deemed unethical to carry out a study in DPB patients receiving no treatment or placebo, it may be more appropriate to conduct RCTs comparing two different kinds of macrolide, or different dosing. The following key points should be considered in future studies: an appropriate comparator therapy, appropriate outcomes (the following categories might be included: mortality, improvements in symptoms, improvements in laboratory results and quality of life) and the cost-effectiveness of the therapy.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akira 1993

Methods	Randomised, parallel-group trial
Participants	<p>Outpatient setting; relevant details of health status of participants, age, sex, country 12 treatment, 7 control 20 to 70 years old (mean, 50 years) Male/female: 9/10 Conducted in Japan</p> <p>All participants met the clinical diagnostic criteria for DPB, among them, the diagnosis of DPB was confirmed by transbronchial lung biopsy (n = 12), open lung biopsy (n = 3) or autopsy (n = 4)</p>
Interventions	12 participants were randomly assigned to receive long-term, low-dose erythromycin (600 mg/d) and 7 assigned to receive no treatment. The duration of the treatment was not clearly described in the report. The trial authors only stated that the patients in the treated group received erythromycin in the period from baseline to follow-up CT scan. The interval between the 2 CT examinations ranged from 4 months to 28 months (mean, 11 months) in the treated group and from 4 months to 72 months (mean, 27 months) in the control group
Outcomes	<p>The outcome reported by the study was changes in CT images. The images were assessed by 2 authors who were blinded to the allocation strategy. DPB in the CT scans was classified into 4 levels:</p> <ul style="list-style-type: none"> • type 1, small nodules around the end of bronchovascular branchings • type 2, small nodules in the centrilobular area of high attenuation • type 3, nodules plus ring-shaped or ductal areas of high attenuation connected to proximal bronchovascular bundles • type 4, large cystic areas of high attenuation plus dilated proximal bronchi <p>Type 1 was the mildest, whereas type 4 was the severest</p>
Notes	None
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Methods of sequence generation were not clearly stated in the included study

Macrolides for diffuse panbronchiolitis (Review)

Akira 1993 (Continued)

Allocation concealment (selection bias)	Unclear risk	Methods of allocation concealment were not clearly stated in the included study
Blinding (performance bias and detection bias) All outcomes	Low risk	The authors did not describe whether the patients were blinded or not. However, they clearly reported that "the CT images were appraised by two observers who did not know which patient received erythromycin therapy". Therefore, we considered that the outcome assessors were blinded. The non-blinding of participants was unlikely to introduce bias as the results were objectively assessed by outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were included in the analysis as there were no drop-outs
Selective reporting (reporting bias)	Unclear risk	The study protocol was not available and there was not sufficient information to draw a conclusion. The risk of bias was therefore unclear
Other bias	High risk	The timing of follow-up was different between the treated group (mean = 11 months) and the control group (mean = 27 months). This might introduce bias. Moreover, the sample size of the study was too small

CT: computerised tomography

DPB: diffuse panbronchiolitis

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Hyeon 1997	It was an observational trial without control group
Kadota 2003	It was an open trial without a control group
Kadota 2004	All patients received long-term macrolide therapy. Not a RCT or quasi-RCT
Kadota 2005	Patients with chronic small airway disease and DPB were enrolled into the study. Not a RCT or quasi-RCT
Kudoh 1984	It was an observational trial without control group
Kudoh 1998	Not a RCT or quasi-RCT
Nagai 1991	It was an observational trial without control group
Sato 1993	Not a RCT or quasi-RCT
Shirai 1997	Not a RCT or quasi-RCT
Yamamoto 1990a	Not a RCT or quasi-RCT
Yamamoto 1992	It was a multicentre, double-blind, placebo-controlled trial. The method of allocation was not clear

DPB: diffuse panbronchiolitis

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Erythromycin versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 The rate of improvement in CT images	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 The rate of progress in CT images	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Erythromycin versus no treatment, Outcome 1 The rate of improvement in CT images.

Study or subgroup	Erythromycin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akira 1993	12/12	0/7		15.38[1.05,225.73]
			Favours control	Favours erythromycin

Analysis 1.2. Comparison 1 Erythromycin versus no treatment, Outcome 2 The rate of progress in CT images.

Study or subgroup	Erythromycin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Akira 1993	0/12	5/7		0.06[0.00,0.88]
			Favours erythromycin	Favours control

APPENDICES

Appendix 1. Previous search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 1), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to April 2010), EMBASE (1974 to April 2010), Chinese Biomedical Literature Database (CBM) (1978 to April 2010), China National Knowledge Infrastructure (CNKI) (1974 to April 2010), KoreaMed (1997 to April 2010) and Database of Japana Centra Revuo Medicina (1983 to April 2010).

We used the following terms to search MEDLINE and CENTRAL. We modified these terms to search the other databases as required. We combined the MEDLINE search string with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE (Lefebvre 2009).

MEDLINE (Ovid)

#1 diffuse panbronchiolitis.tw.

#2 DPB.tw.

#3 1 or 2

#4 exp Macrolides/

#5 (macrolide* or clarithromycin* or troleandomycin* or erythromycin* or josamycin* or azithromycin* or roxithromycin*).tw.

#6 4 or 5

#7 3 and 6

See [Appendix 3](#), [Appendix 4](#), [Appendix 5](#), [Appendix 6](#) and [Appendix 7](#) for individual search strategies for each database.

In the 2012 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 7, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 25 July 2012), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (March 2010 to July 2012), EMBASE (March 2010 to July 2012), Chinese Biomedical Literature Database (CBM) (1978 to July 2012), China National Knowledge Infrastructure (CNKI) (1974 to July 2012), KoreaMed (2010 to July 2012) and Database of Japan's Centre for Reviews and Medicines (1983 to July 2012).

We used the following search strategy to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format (Lefebvre 2011). We modified these terms to search the other databases as required.

MEDLINE (Ovid)

```
1 (panbronchiolitis or pan-bronchiolitis).tw,ot.
2 diffuse panbronchiolitis.rs.
3 dpb.tw.
4 or/1-3
5 exp Macrolides/
6 macrolide*.tw,nm.
7 (macrolide* or clarithromycin* or troleandomycin* or erythromycin* or josamycin* or azithromycin* or roxithromycin*).tw,nm.
8 Anti-Bacterial Agents/
9 or/5-8
10 4 and 9
```

Appendix 2. MEDLINE (Ovid) search strategy

```
1 (panbronchiolitis or pan-bronchiolitis).tw,ot.
2 diffuse panbronchiolitis.rs.
3 dpb.tw.
4 or/1-3
5 exp Macrolides/
6 macrolide*.tw,nm.
7 (macrolide* or clarithromycin* or troleandomycin* or erythromycin* or josamycin* or azithromycin* or roxithromycin*).tw,nm.
8 Anti-Bacterial Agents/
9 or/5-8
10 4 and 9
```

Appendix 3. EMBASE (Elsevier) search strategy

```
#15 #6 AND #14
#14 #9 NOT #13
#13 #10 NOT #12
#12 #10 AND #11
#11 'human'/de
#10 'animal'/de OR 'animal experiment'/de OR 'nonhuman'/exp
#9 #7 OR #8
#8 random*:ab,ti OR placebo*:ab,ti OR allocat*:ab,ti OR trial:ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR (doubl* NEXT/1 blind*):ab,ti
#7 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#6 #1 AND #5
#5 #2 OR #3 OR #4
#4 'antibiotic agent'/de
#3 macrolide*:ab,ti OR clarithromycin*:ab,ti OR troleandomycin*:ab,ti OR erythromycin*:ab,ti OR josamycin*:ab,ti OR azithromycin*:ab,ti
OR roxithromycin*:ab,ti
#2 'macrolide'/exp
#1 panbronchiolitis:ab,ti OR 'pan-bronchiolitis':ab,ti OR dpb:ab,ti
```

Appendix 4. CBM search strategy (in Chinese)

```
#1 diffuse panbronchiolitis
#2 DPB
#3 1 or 2
#4 "Macrolides"/exp
#5 macrolide or clarithromycin or troleandomycin or erythromycin or josamycin or azithromycin or roxithromycin
#6 4 or 5
#7 3 and 6
```

Appendix 5. CNKI search strategy (in Chinese)

#1 diffuse panbronchiolitis

#2 DPB

#3 1 or 2

#4 "Macrolides"/exp

#5 macrolide or clarithromycin or troleandomycin or erythromycin or josamycin or azithromycin or roxithromycin

#6 4 or 5

#7 3 and 6

Appendix 6. KoreaMed search strategy (via www.koreamed.org)

(diffuse panbronchiolitis or DPB) and (macrolide* or clarithromycin* or troleandomycin* or erythromycin* or josamycin* or azithromycin* or roxithromycin*)

Appendix 7. Database of Japana Centra Revuo Medicina search strategy (in Japanese)

(diffuse panbronchiolitis or DPB) and (macrolide* or clarithromycin* or troleandomycin* or erythromycin* or josamycin* or azithromycin* or roxithromycin*)

WHAT'S NEW

Date	Event	Description
15 July 2014	New citation required but conclusions have not changed	Our conclusions remain unchanged.
15 July 2014	New search has been performed	We did not identify any new trials for inclusion or exclusion.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 12, 2010

Date	Event	Description
25 July 2012	New search has been performed	New searches conducted
25 July 2012	New citation required but conclusions have not changed	New searches conducted and content updated.
25 July 2012	New search has been performed	We did not identify any new trials for inclusion or exclusion.

CONTRIBUTIONS OF AUTHORS

All authors have contributed to this review.

XF Lin (XFL) and M Yang (MY) searched the databases, extracted the data and reformed the tables.

MY and J Lu (JL) screened trials. In the 2014 updated version, XFL and JL screened trials.

MY and JL appraised the quality of included trials and drafted the manuscript.

BR Dong (BRD) and HM Wu (HMW) were responsible for improving the manuscript.

BRD also acted as an arbitrator. In the 2014 updated version, MY acted as an arbitrator.

DECLARATIONS OF INTEREST

Xiufang Lin: none known

Jing Lu: none known

Ming Yang: none known

Macrolides for diffuse panbronchiolitis (Review)

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Bi Rong Dong: none known

Hong Mei Wu: none known

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Center, Chinese Centre of Evidence-Based Medicine, West China Hospital of Sichuan University, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Bronchiolitis [diagnostic imaging] [*drug therapy]; Erythromycin [*therapeutic use]; Haemophilus Infections [diagnostic imaging] [*drug therapy]; Macrolides [therapeutic use]; Randomized Controlled Trials as Topic; Tomography, X-Ray Computed

MeSH check words

Humans