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Antibiotic treatment for Stenotrophomonas maltophilia in people with cystic fibrosis (Review)

Amin R, Waters V

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TABLE OF CONTENTS

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[Intervention Review]

Antibiotic treatment for *Stenotrophomonas maltophilia* in people with cystic fibrosis

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ABSTRACT

Background

Stenotrophomonas maltophilia is one of the most common emerging multi-drug resistant organisms found in the lungs of people with cystic fibrosis and its prevalence is increasing. Chronic infection with *Stenotrophomonas maltophilia* has recently been shown to be an independent predictor of pulmonary exacerbation requiring hospitalization and antibiotics. However, the role of antibiotic treatment of *Stenotrophomonas maltophilia* infection in people with cystic fibrosis is still unclear. This is an update of a previously published review.

Objectives

The objective of our review is to assess the effectiveness of antibiotic treatment for *Stenotrophomonas maltophilia* in people with cystic fibrosis. The primary objective is to assess this in relation to lung function and pulmonary exacerbations in the setting of acute pulmonary exacerbations. The secondary objective is to assess this in relation to the eradication of *Stenotrophomonas maltophilia*.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched a registry of ongoing trials and the reference lists of relevant articles and reviews.

Date of latest search: 27 May 2016.

Selection criteria

Any randomized controlled trial of *Stenotrophomonas maltophilia* mono-infection or *Stenotrophomonas maltophilia* co-infection with *Pseudomonas aeruginosa* in either the setting of an acute pulmonary exacerbation or a chronic infection treated with suppressive antibiotic therapy.

Data collection and analysis

Both authors independently assessed the trials identified by the search for potential inclusion in the review.

Main results

The initial search strategy identified only one trial of antibiotic treatment of pulmonary exacerbations that included people with cystic fibrosis with *Stenotrophomonas maltophilia*. However, this trial had to be excluded because data was not available per pathogen.

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Authors' conclusions

This review did not identify any evidence regarding the effectiveness of antibiotic treatment for *Stenotrophomonas maltophilia* in people with cystic fibrosis. Until such evidence becomes available, clinicians need to use their clinical judgement as to whether or not to treat *Stenotrophomonas maltophilia* infection in people with cystic fibrosis. Randomized clinical trials are needed to address these unanswered clinical questions.

PLAIN LANGUAGE SUMMARY

Antibiotic treatment for *Stenotrophomonas maltophilia* in people with cystic fibrosis

Review question

We reviewed the evidence about the effect of antibiotics in people with cystic fibrosis who were infected with *Stenotrophomonas maltophilia*.

Background

Stenotrophomonas maltophilia is a bacterium which is resistant to several antibiotics and over the last 10 years it has increasingly been found in the lungs of people with cystic fibrosis. Chronic infection with *Stenotrophomonas maltophilia* has been found to be linked to pulmonary infections. However, at present, it is unclear if people with cystic fibrosis should be treated for this pulmonary infection when it is identified. The purpose of this review is to determine whether treatment with different antibiotic combinations for *Stenotrophomonas maltophilia* will improve lung function or decrease the frequency of hospital admission in people with cystic fibrosis. We also want to review the effect of treatment of chronic *Stenotrophomonas maltophilia* infection for the purposes of eradication from the lungs of a person with cystic fibrosis. This is an update of a previously published review.

Search date

The evidence is current to: 27 May 2016.

Trial characteristics

We did not find any randomized controlled trials (trials where the people taking part are put into different treatment groups completely at random) which we could include in the review. We did find one trial of antibiotic treatment for pulmonary exacerbations (flare up of disease in the airways) which included people infected with *Stenotrophomonas maltophilia*, but the people in the trial also had infections caused by other bacteria and we were not able to obtain separate data for the different causes of infection.

Key results

Randomized controlled trials are needed to inform clinicians as to whether they should treat *Stenotrophomonas maltophilia* infection in people with cystic fibrosis. In the meantime, clinicians should use their clinical judgement when considering this question.

BACKGROUND

Description of the condition

Respiratory failure secondary to chronic bacterial respiratory infection is the leading cause of death in cystic fibrosis (CF) (Gibson 2003). As people with CF are living longer, more are being infected with multi-drug resistant pathogens in their airways. Among these, *Stenotrophomonas maltophilia* (*S. maltophilia*) is one of the most common (Steinkamp 2005). This multi-drug resistant gram-negative bacterium (previously known as *Xanthomonas maltophilia*) has been increasingly isolated worldwide as a cause of serious infections (Denton 1998b; Hanes 2002; Kagen 2007; Muder 1996; Paez 2008; Senol 2002; Tsai 2006). The pathogen *S. maltophilia* has been isolated from the respiratory tracts of 8% of people with

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CF in Canada (CF Registry Data 2002), 10% in the USA (CF Registry Data 2003) and ranges from 4% to 30% at CF clinics in Europe (Ballestero 1995; Gibson 2003; Millar 2009). This variability in prevalence may reflect differences in ability to identify the organism in different clinical laboratories.

Risk factors for the isolation of *S. maltophilia* in the respiratory tract of people with CF include intravenous antibiotic use and oral quinolone antibiotic use (Graff 2002; Marchac 2004; Talmaciu 2000). In a retrospective case-control study, the use of anti-pseudomonal antibiotics was associated with *S. maltophilia* isolation in the respiratory tract (Denton 1998a).This prompts the question whether aggressive antibiotic treatment, especially for *Pseudomonas aeruginosa* (*P. aeruginosa*) may be promoting *S. maltophilia* colonization.

It has been unclear whether *S. maltophilia* simply colonizes the lungs of people with CF without adverse effect or causes true infection leading to pulmonary inflammation and clinical deterioration. A retrospective cohort study using the Toronto CF database demonstrated that, even after adjusting for markers of lung disease severity, chronic *S. maltophilia* infection in people with CF was an independent risk factor for pulmonary exacerbation requiring hospitalization and antibiotics and was associated with a systemic immune response to *S. maltophilia*, suggesting true infection (Waters 2011). Antibiotic treatment of *S. maltophilia* in people with CF may thus be indicated. However, other studies have demonstrated that the isolation of *S. maltophilia* from the respiratory tract of individuals with CF is not associated with decreased survival or worse lung function (Goss 2002; Goss 2004).

Antibiotics have been successful in treating respiratory infections in CF, but it is still unclear whether these treatments will have an effect in the case of *S. maltophilia*, in both the acute and chronic setting.

Description of the intervention

While *S. maltophilia* has many mechanisms of antimicrobial resistance, *in vitro* it appears to be most susceptible to trimethoprim-sulfamethoxazole, levofloxacin, ticarcillin-clavulanate and doxycycline (Denton 1998b; San Gabriel 2004). When treating *S. maltophilia* during an acute pulmonary exacerbation, two intravenous antibiotics would generally be chosen based on antimicrobial susceptibility testing results. Trimethoprim-sulfamethoxazole, levofloxacin and doxycycline are also available in oral formulations and can thus be used to treat less severe pulmonary exacerbations due to *S. maltophilia* in an outpatient setting. At present there are no antibiotic regimens in place for chronic suppressive therapy although aerosolized levofloxacin may be a potential future option.

How the intervention might work

Over the past several decades, the life expectancy of people with CF has increased significantly, due partly to the aggressive use of antibiotics in the treatment of respiratory infections (Gibson 2003; Johnson 2003). Antibiotic therapy can be used in different ways to treat people with CF. Intravenous antibiotic use is the standard of care for the treatment of acute pulmonary exacerbations (VanDevanter 2010). Antibiotics are used in the following circumstances:

1. for acute exacerbations (oral or intravenous depending on severity);
2. for eradication of first isolates;
3. for chronic suppression therapy.

Antibiotics can also be used to suppress the growth of bacteria in the lung and improve pulmonary function in people with CF with chronic infection, such as the use of inhaled tobramycin to treat people with CF who have chronic *P. aeruginosa* infection (Ramsey 1999). It is unclear whether antibiotic treatment of *S. maltophilia* during acute pulmonary exacerbations or as suppressive antibiotic therapy for chronic infection has similar effects on clinical or microbiological outcomes in CF.

Why it is important to do this review

At present there are no clear guidelines or published reviews to aid clinicians with respect to the management of *S. maltophilia* in people with CF. In light of these uncertainties, we aim to compare antibiotics to treat *S. maltophilia* compared to no antibiotics to treat *S. maltophilia.* We will also compare one antibiotic regimen to another antibiotic regimen for treating *S. maltophilia.* These two antibiotic strategies will be compared in two different settings which include acute pulmonary exacerbations and suppressive antibiotic therapy, in people with CF. It is not known, however, if antibiotic treatment for *S. maltophilia* in people with CF affects their outcome.

This is an update of a previously published version of the review (Amin 2012; Amin 2014).

OBJECTIVES

The objective of our review is to assess the effectiveness of antibiotic treatment for *S. maltophilia* in people with CF. The primary objective is to assess this in relation to lung function and pulmonary exacerbations in the setting of acute pulmonary exacerbations and suppressive antibiotic therapy. The secondary objective is to assess this in relation to the eradication of *S. maltophilia*.

METHODS

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Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children (with all levels of disease severity) with a clinical diagnosis of CF, confirmed with sweat test or genetic testing or both, who have *S. maltophilia* isolated from respiratory specimens. If a clinical diagnosis of CF is not met, these participants will be excluded.

Types of interventions

The intervention will be antibiotic therapy used to treat *S. maltophilia* cultured in a respiratory tract specimen from people with CF. Respiratory tract specimens will include sputum, throat swabs or bronchoalveolar lavage specimens. Antibiotic therapy will include oral, intravenous or inhaled antibiotics. We will compare antibiotics to treat *S. maltophilia* compared to no antibiotics to treat *S. maltophilia* or one antibiotic regimen compared to another antibiotic regimen to treat *S. maltophilia* in people with CF.

We will investigate the antibiotic treatment for *S. maltophilia* in CF in two settings. For each setting, we will subdivide into two groups: *S. maltophilia* mono-infection and *S. maltophilia* co-infection with *P. aeruginosa*. The first setting will be antibiotics used to treat acute pulmonary exacerbations. An acute pulmonary exacerbation will be defined according to symptoms, chest examination findings and change in forced expiratory volume in one second (Rosenfeld 2001). The second setting will be the use of long-term antibiotics to treat *S. maltophilia* in CF as a suppressive treatment. Long-term suppressive treatment will be defined as antibiotic therapy longer than four weeks outside the setting of an acute pulmonary exacerbation. A subgroup analysis will be performed for the different types (oral, inhaled and intravenous) of antibiotic administration.

Types of outcome measures

Acute pulmonary exacerbations

Primary outcomes

1. Lung function
   i) forced expiratory volume at one second (FEV_1) (absolute values litres or per cent (%) predicted or both)
   ii) forced vital capacity (FVC) (absolute values litres or % predicted or both)
   iii) mid-expiratory flow ($FEF_{25–75}$) (absolute values litres or % predicted or both)
2. Pulmonary exacerbations
   i) number of days until next exacerbation
   ii) length of hospital stay
3. Adverse events
   i) emergence of resistant organisms
   ii) other adverse events such as rashes, Stevens-Johnson type reactions, photosensitivity, tooth discolouration etc

Secondary outcomes

1. Quality of life (QOL) (as measured by a validated QOL score i.e. CFQoL (Gee 2000), CFQ-R (Quittner 2009))
2. Sputum bacterial density measured in colony forming units/ml (CFU/ml)
3. Nutrition
   i) weight
   ii) body mass index (BMI)
4. Symptom score
5. Mortality

Chronic suppressive therapy

Primary outcome

1. Lung function
   i) FEV_1 (absolute values litres or % predicted or both)
   ii) FVC (absolute values litres or % predicted or both)
   iii) $FEF_{25–75}$ (absolute values litres or % predicted or both)
2. Pulmonary exacerbations
   i) number of days until next exacerbation
   ii) length of hospital stay
   iii) risk of pulmonary exacerbation
3. Adverse events
   i) emergence of resistant organisms
   ii) other adverse events such as rashes, Stevens-Johnson type reactions, photosensitivity, tooth discolouration etc

Secondary Outcomes

1. QOL (as measured by a validated QoL score i.e. CFQoL (Gee 2000), CFQ-R (Quittner 2009))
2. Sputum bacterial density measured in CFU/ml
3. Nutrition
   i) weight
   ii) BMI
4. Symptom score
5. Mortality

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Search methods for identification of studies

Electronic searches

We searched for relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (*Stenotrophomonas maltophilia* or mixed infections) AND (acute treatment OR unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group Module.

Date of last search of CF Trials Register: 27 May 2016.

We also checked the National Institutes of Health (NIH) sponsored web site www.clinicaltrials.gov for any ongoing trials with potential interim results using the keywords: *Stenotrophomonas maltophilia* and cystic fibrosis.

Date of last search: 15 June 2016.

Searching other resources

In future, we will check the reference lists of all trials identified for any further relevant trials. In addition, we will contact experts in the field and the authors of any included trials to ask if they are aware of any ongoing trials.

Data collection and analysis

We were not able to include any trials in this version of the review. However, for future updates, if we are able to include relevant trials, we will undertake analysis as described below. For further details of methodological terms see the Cochrane Glossary.

Selection of studies

We (RA, VW) will independently apply the inclusion criteria to all potential trials. We will not be blinded to the trials. If a disagreement occurs, we will resolve this by discussion with a third person (Felix Ratjen (FR)).

Data extraction and management

Using a data collection form, we (RA, VW) will independently obtain data from published reports or from trial investigators. If a disagreement occurs, we will resolve this by discussion with a third person (FR). In addition to information about trial references and authors and verification of trial eligibility, the data collection form will include information about the methods of the trial (e.g. trial duration, type of trial, blinding, number of dropouts and potential confounders). We will also report characteristics of the trial participants including age, sex and setting of the trial on the form. Furthermore, we will also describe the intervention with regards to type of antibiotic, route of delivery, doses and length of treatment. We will collect data for all randomized participants. When possible we will collect the following data: the mean change (before and after antibiotic therapy) in FEV_1 and FVC, FEF_{25-75}; the mean QOL score after antibiotic therapy; the mean hospital length of stay; the mean change in sputum bacterial density (before and after antibiotic therapy); and the number of adverse events and mortalities. For each mean value, we will also obtain the standard deviation (SD). For time to next exacerbation, we will collect estimates from log-rank tests and cox proportional hazards modelling methods.

We plan to measure outcomes at less than a week, one to two weeks, more than two weeks to three weeks, more than three weeks to four weeks and at monthly intervals, if applicable in the acute pulmonary exacerbation setting. In the setting of chronic suppressive therapy, we will measure outcomes at monthly intervals. We will measure the time to next pulmonary exacerbation in monthly intervals after these time points. We will also consider outcomes measured at other time points.

Assessment of risk of bias in included studies

We will assess the included trials for the following types of bias: selection bias; performance bias; attrition bias; detection bias; and reporting bias (Higgins 2011a) using the following strategies as outlined below. We will assess the blinding separately for different outcome measures. For further details of methodological terms see the Cochrane Glossary.

Assessment of generation of allocation sequences

We will assess each trial as to the generation of allocation sequences:

1. low risk of bias: if allocation sequence is suitable to prevent selection bias (i.e. random numbers table, drawing envelopes, tossing a coin, throwing dice etc);
2. high risk of bias: if allocation sequence could be related to prognosis and thus introduce selection bias (i.e. assigning participants based on case record number, date of birth, date of admission etc);
3. unclear risk of bias: if the trial is described as randomised but the method used to generate the allocation sequence is not stated.

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Assessment of concealment of allocation sequences

We will also assess the method used to conceal the allocation sequences in each trial:

1. low risk of bias: if participants and investigators cannot predict which group the participant will be assigned to (i.e. coded drug containers, central randomisation, numbered, sealed, opaque envelopes etc);
2. high risk of bias: if participants and investigators can predict which group the participant will be assigned to and thus introduce selection bias (i.e. open allocation schedule, non-opaque envelopes etc);
3. unclear risk of bias: if the method of concealing the allocation sequence is not described.

Assessment of blinding

In order to determine the potential for performance and detection bias, we will assess each trial with respect to the degree of blinding:

1. the participant is blinded to participant assignment;
2. the care provider is blinded to participant assignment;
3. the investigator measuring trial outcomes is blinded to participant assignment.

There will be a high risk of bias if there is no blinding with respect to one or more of the above categories. There will be a low risk of bias if the trial is blinded to all three. There will be an unclear risk of bias if the trial does not specify the degree of blinding in each of the three categories.

Incomplete outcome data

To assess for the possibility of attrition bias, we will examine each trial with respect to:

1. whether or not it was stated how many participants were lost to follow-up and why they were lost to follow-up;
2. whether or not an intention-to-treat analysis was used (i.e. inclusion in the final analysis of all randomized participants into a trial in the groups to which they were randomized irrespective of what happened subsequently).

There will be a high risk of bias if an intention-to-treat analysis was not used. There will be a low risk of bias if the number and reason for loss of follow-up is specified and if an intention-to-treat analysis was used. There will be an unclear risk of bias if the trial does not specify the above outlined information.

Assessment of selective reporting

We will review the included trials for selective reporting (Higgins 2011a). We will compare the original trial protocols with the published paper(s) to ensure all planned outcomes are reported. If the original trial protocols are not available, we will review the 'Methods' and 'Results' sections and the authors will use their discretion to determine if selective reporting has occurred.

Assessment of other potential sources of bias

We will also review the included trials for other potential sources of bias that will threaten the validity of the trial. These will include: early cessation of the trial; if the interim results affect the trial conduct; deviation from the trial protocol; inappropriate administration of a co-intervention; contamination; the use of an insensitive instrument to measure outcomes; selective reporting of subgroups; fraud; inappropriate influence of funding agencies and industry sponsorship; null bias due to the interventions being poorly delivered; or the existence of a pre-randomization of an intervention that could affect the effects of the randomized intervention (Higgins 2011a).

Incorporating assessments of trial validity in reviews

We plan to give weight to trials according to their assessed validity by using the inverse of the variance for the estimated measure of effect. If we consider there was a high risk of bias, we will investigate the effects of this with a sensitivity analysis (see below).

Measures of treatment effect

For dichotomous data, we will gather information on participants randomized to each treatment group, based on an intention-to-treat analysis, and the number of events. We plan to include interim results from individual randomised participants from ongoing trials in the analysis. We will define time-points for each trial outcome according to when it was measured (less than a week, one to two weeks, more than two weeks to three weeks, more than three weeks to four weeks and at monthly intervals for acute pulmonary exacerbations and monthly intervals for chronic suppressive therapy). We will analyse trial outcomes separately according to these time-points. We plan to pool the treatment effect across trials to determine an odds ratio (OR) and its 95% confidence intervals (CIs).

For continuous data, we will calculate the difference between the mean values (MD) and SD of treatment effect for each group. As a summary statistic across trials, we will use the MD if the same scale is used, or the standardised mean difference (SMD) if different scales are used (e.g. quality of life measurements) both with 95% CIs. For time-to-event data, most trials use Kaplan-Meier survival analysis. We will thus collect log-rank estimates and Cox-model estimates to subsequently summarize the time-to-event data as a hazard ratio (HR) with 95% CIs (Higgins 2011b; Parmar 1998).

Unit of analysis issues

We will include data from cluster-randomized trials if the information is available. For clusterrandomized trials, we will calculate the intracluster correlation coefficient (ICC) according to Donner (Donner 2001). We will also include data from cross-over trials if the information is available. We will analyze continuous data

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from cross-over trials using one of three approaches: treat the trial as a parallel trial and pool the interventional periods and compare these to the pooled placebo periods; include data from the first period only and approximate a paired analysis; by imputing missing SDs (Higgins 2011c). Cross-over trials with dichotomous outcomes require more complicated methods and we will consult with a statistician as recommended (Elbourne 2002).

Dealing with missing data

Data are often missing for participants who are lost to follow-up. We will perform an available-case analysis (analysing data for every participant for whom the outcome data are obtained) in these situations. We will report the percentages of participants from whom no outcome data were obtained on the data collection form. We will include data on only those whose results are known, using as a denominator the total number of people who completed the trial for the particular outcome in question. We will consider variation in the degree of missing data across trials as a potential source of heterogeneity. We will contact trial authors for the missing data.

Assessment of heterogeneity

In performing a meta-analysis, we will measure the variability of results between trials (heterogeneity) using the I^2 method outlined by Higgins (Higgins 2003). The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than by chance. It is calculated using Cochran's heterogeneity statistic and the degrees of freedom. The I^2 statistic can range from 0 to 100%. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity. A value greater than 50% may be considered substantial heterogeneity (Higgins 2011b).

Assessment of reporting biases

To investigate whether this review is subject to publication bias, we will construct a funnel plot, if we are able to include sufficient trials (at least 10). In the absence of bias, the plot should resemble a symmetrical inverted funnel (Higgins 2011d). If there is asymmetry, we will consider publication bias and other reasons (such as location biases, true heterogeneity, a high risk of bias of smaller trials, outcome reporting bias etc.) as potential causes.

Data synthesis

We plan to combine multiple trials as follows. If the trials are too clinically diverse (e.g. different antibiotic doses), we will not combine these trials and will not perform a meta-analysis. If however, the trials are considered clinically similar (e.g. pulmonary exacerbation trials with different types of antibiotics, oral versus intravenous, with different lengths of treatment) enough to combine, statistical heterogeneity will be investigated as outlined below.

Depending on the results of our assessment of heterogeneity, the authors will use a fixed-effect model for a low degree of heterogeneity, i.e. if the I^2 statistic is up to 40%, and a random-effects analysis for a moderate or high degree of heterogeneity, i.e. if the I^2 statistic is over 40% (Higgins 2011b).

Subgroup analysis and investigation of heterogeneity

If we include sufficient trials (at least 10) and find significant heterogeneity ($P < 0.10$ by Chi^2 test) (Deeks 2001), we will explore the potential causes of this (i.e. different types of antimicrobial treatment, different participant populations etc.) and if possible, we plan to undertake four subgroup analyses:

1. comparison of chronically co-infected participants versus those never affected;
2. comparison of chronically infected participants with *S. maltophilia* only versus those never affected;
3. a comparison of the pediatric and adult population (results may vary if one trial has more adult participants who can produce sputum (a more accurate sample with potentially more reliable culture results) and another trial has more pediatric participants who can only do throat swabs (a less reliable respiratory tract sample));
4. comparison of different types of antibiotic treatments used (e.g. trimethoprim-sulfamethoxazole compared to levofloxacin).

Sensitivity analysis

If we include at least 10 trials in the review, we will perform a sensitivity analysis to determine whether the conclusions are robust to decisions made during the review process. We will perform the analysis:

- both with and without quasi-randomized trials;
- including and then excluding trials with a high risk of bias in one or more aspects;
- analysing the data using a random-effects model and a fixed-effect model;
- analysing the data both with and without outlier trials (trial with mean outcome measure more than two SD compared to mean outcome measure in all other trials combined);
- including and excluding trials that have been published more than once
- including and excluding parallel and cross-over trials.

We will investigate whether changing any of these decisions made during the review process changes the conclusions of our review. If the sensitivity analysis does not significantly change the results, it strengthens the confidence that can be placed in these results. We will present all trials and provide a narrative discussion of the risk of bias.

RESULTS

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Description of studies

Results of the search

The search identified four trials of antibiotic treatment of pulmonary exacerbations that potentially included people with CF with *S. maltophilia*; all of these were excluded.

Included studies

No trials met the inclusion criteria for this review.

Excluded studies

Two trials that included people with *S. maltophilia* were excluded because data were not available based on individual pathogens (Aaron 2005; Prayle 2013). The lead author of the Aaron trial confirmed this in previous correspondence. In one trial, the inclusion criteria were for participants to just be *Pseudomonas aeruginosa* negative and not *S. maltophilia* positive (Singh 2013). The inclusion criteria for the fourth trial also did not specify that participants were *S. maltophilia* positive (Stockmann 2015).

Risk of bias in included studies

No trials met the inclusion criteria for this review, therefore there were no trials for which risk of bias could be assessed.

Effects of interventions

No trials met the inclusion criteria for this review, therefore the effectiveness of antibiotic treatment for *S. maltophilia* in people with CF could not be assessed.

DISCUSSION

Summary of main results

No randomized controlled trials were identified which met the inclusion criteria for this review. Trials were excluded as data were not available by pathogen (Aaron 2005; Prayle 2013) or their inclusion criteria did not state that participants tested positive for *Stenotrophomonas maltophilia* (*S. maltophilia*) (Singh 2013; Stockmann 2015). In the absence of direct evaluation of different treatment combinations for *S. maltophilia* and their subsequent outcomes in both acute and chronic settings, what other issues should be considered by clinicians when deciding on therapy?

Agreements and disagreements with other studies or reviews

Chronic infection with *S. maltophilia* is more likely to cause negative clinical consequences in individuals with cystic fibrosis (CF) than intermittent infection and several trials have thus attempted to determine the impact of chronic *S. maltophilia* infection on CF lung disease. In a large retrospective cohort study using the Toronto CF Database, it has been shown that, even after adjusting for markers of lung disease severity, chronic *S. maltophilia* infection in people with CF was an independent risk factor for pulmonary exacerbation requiring hospitalization and antibiotics as compared to those that were not chronically infected (Waters 2011). People who were intermittently infected did not have an increased risk and there was no difference in the rate of decline in FEV_1 amongst the groups (Waters 2011). Another recent retrospective cohort study showed that people with chronic *S. maltophilia* infection had a steeper rate of decline in FEV_1 than uninfected CF controls, but not steeper than before the chronic infection (Dalboge 2011). However, this small study was underpowered to detect differences in FEV_1 and did not adjust for potential confounding variables. These studies suggest that *S. maltophilia* may be causing harm in some people with CF and can no longer be ignored as a potential pathogen in CF. Treatment of this organism in the setting of acute pulmonary exacerbations and chronic infection may thus be warranted, but randomized controlled trials evaluating such treatment are clearly lacking. The only published evidence for the role of antibiotic treatment of *S. maltophilia* in CF is in the form of a retrospective cohort study (Waters 2012). In a multiple regression model, chronic *S. maltophilia* infection and number of days of antibiotic therapy against *S. maltophilia* during a pulmonary exacerbation was not associated with a significant difference in the FEV_1 recovery or with a difference in time to subsequent pulmonary exacerbation. It is important to note, however, that almost all participants were treated with only one antimicrobial drug targeting *S. maltophilia*, to which the organism can rapidly develop resistance to (Brooke 2012), and resulted in elimination of *S. maltophilia* from the airways in only one quarter of chronic *S. maltophilia* pulmonary exacerbations. This raises the question of whether the antimicrobial treatment of *S. maltophilia* in the remaining three-quarters of participants was truly effective. As such, further understanding of the role of antibiotic treatment of *S. maltophilia* and the clinical consequences is paramount for people with CF.

Until further evidence is available, clinicians need to consider therapy for people with CF with positive respiratory cultures for *S. maltophilia* on a case by case basis. Newer non-culture based techniques such as 16S rRNA gene sequencing may further clarify the role of *S. maltophilia* within the complex microbiome of the CF lung (Rogers 2003).

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AUTHORS' CONCLUSIONS

Implications for practice

This review did not identify any evidence regarding the effectiveness of antibiotic treatment for *S. maltophilia* in people with CF in the setting of a pulmonary exacerbation. Until such evidence becomes available, clinicians need to use their clinical judgement as to whether or not to treat *S. maltophilia* infection in people with CF experiencing pulmonary exacerbations both in the setting of *S. maltophilia* mono-infection as well as co-infection.

This review also did not identify any evidence regarding the effectiveness of antibiotic treatment for *S. maltophilia* in people with CF with chronic infection. Until such evidence becomes available, clinicians need to use their clinical judgement as to whether or not to treat *S. maltophilia* infection in people with CF in the setting of chronic infection.

Implications for research

Given the limited knowledge on the effectiveness of antibiotic treatment for *S. maltophilia* infection in people with CF, properly designed and adequately powered randomized controlled trials are needed to determine if antibiotic treatment during acute pulmonary infections in the setting of mono-infection and co-infection with *S. maltophilia* improves microbiological outcomes (such as sputum bacterial density) and clinical outcomes (such as time to next pulmonary exacerbation) in people with CF. Similarly, properly designed and adequately powered randomized controlled trials are needed to determine if antibiotic treatment for chronic infection of *S. maltophilia* improves clinical outcomes (such as forced expiratory volume in one second (FEV_1)) in people with CF.

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We wish to thank Nikki Jahnke and Tracey Remmington for their assistance in the preparation of this review.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Aaron 2005	Data not available for individual pathogens.
Prayle 2013	Data not available for individual pathogens.
Singh 2013	The inclusion criteria for the trial was not *Stenotrophomonas maltophilia* positive just *Pseudomonas aeruginosa* negative.
Stockmann 2015	This trial considers the use of levofloxacin inhalation for the treatment of chronic *Pseudomonas aeruginosa*. The trial was excluded on the basis of the inclusion criteria as participants were not *Stenotrophomonas maltophilia* positive.

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DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 12 July 2016.

Date	Event	Description
12 July 2016	New citation required but conclusions have not changed	No new data were included in this updated review, therefore our conclusions remain the same
12 July 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified six new references to three unique trials, none of which were eligible for inclusion in this review (Prayle 2013; Singh 2013; Stockmann 2015).

HISTORY

Protocol first published: Issue 7, 2011

Review first published: Issue 5, 2012

Date	Event	Description
13 April 2015	Amended	Contact details updated.
2 April 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Group's Cystic Fibrosis Trials Register did not identify any new trials potentially eligible for inclusion in this review
2 April 2014	New citation required but conclusions have not changed	No new trials have been included in the review hence our conclusions remain unchanged

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CONTRIBUTIONS OF AUTHORS

TASK	WHO WILL UNDERTAKE THE TASK?
Protocol stage: draft the protocol	Reshma Amin and Valerie Waters
Review stage: select which trials to include (2 + 1 arbiter)	Reshma Amin and Valerie Waters (+ Felix Ratjen)
Review stage: extract data from trials (2 people)	Reshma Amin and Valerie Waters
Review stage: enter data into RevMan	Reshma Amin and Valerie Waters
Review stage: carry out the analysis	Reshma Amin and Valerie Waters
Review stage: interpret the analysis	Reshma Amin and Valerie Waters
Review stage: draft the final review	Reshma Amin and Valerie Waters
Update stage: update the review	Reshma Amin and Valerie Waters

DECLARATIONS OF INTEREST

Reshma Amin declares she has received funding from Novartis for an investigator-run clinical trial which is **OUTSIDE** the scope of this Cochrane review.

Val Waters declares that Innvotech Inc funded the biofilm trial; a randomized controlled trial of the use of biofilm antimicrobial susceptibility testing in CF on which she worked. She also has received a CF Canada grant to investigate the role of epidemic *Pseudomonas aeruginosa* in CF.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Stenotrophomonas maltophilia; Anti-Bacterial Agents [*therapeutic use]; Cystic Fibrosis [*complications; microbiology]; Gram-Negative Bacterial Infections [*drug therapy; microbiology]; Respiratory Tract Infections [*drug therapy; microbiology]

MeSH check words

Humans

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