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Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis (Review)

Waters V, Ratjen F

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[Intervention Review]

Antibiotic treatment for nontuberculous mycobacteria lung infection in people with cystic fibrosis

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ABSTRACT

Background

Nontuberculous mycobacteria are mycobacteria, other than those in the *Mycobacterium tuberculosis* complex, and are commonly found in the environment. Nontuberculous mycobacteria species (most commonly *Mycobacterium avium* complex and *Mycobacterium abscessus*) are isolated from the respiratory tract of approximately 5% to 40% of individuals with cystic fibrosis; they can cause lung disease in people with cystic fibrosis leading to more a rapid decline in lung function and even death in certain circumstances. Although there are guidelines for the antimicrobial treatment of nontuberculous mycobacteria lung disease, these recommendations are not specific for people with cystic fibrosis and it is not clear which antibiotic regimen may be the most effective in the treatment of these individuals. This is an update of a previous review.

Objectives

The objective of our review was to compare antibiotic treatment to no antibiotic treatment, or to compare different combinations of antibiotic treatment, for nontuberculous mycobacteria lung infections in people with cystic fibrosis. The primary objective was to assess the effect of treatment on lung function and pulmonary exacerbations and to quantify adverse events. The secondary objectives were to assess treatment effects on the amount of bacteria in the sputum, quality of life, mortality, nutritional parameters, hospitalizations and use of oral antibiotics.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and hand searching of journals and conference abstract books. Date of last search: 02 September 2016.

We also searched a register of ongoing trials and the reference lists of relevant articles and reviews. Date of last search: 03 November 2016.

Selection criteria

Any randomized controlled trials comparing nontuberculous mycobacteria antibiotics to no antibiotic treatment, as well as one nontuberculous mycobacteria antibiotic regimen compared to another nontuberculous mycobacteria antibiotic regimen, in individuals with cystic fibrosis.

Data collection and analysis

Data were not collected because in the one trial identified by the search, data specific to individuals with cystic fibrosis could not be obtained from the pharmaceutical company.

Main results

One completed trial was identified by the searches, but data specific to individuals with cystic fibrosis could not be obtained from the pharmaceutical company.

Authors' conclusions

This review did not find any evidence for the effectiveness of different antimicrobial treatment for nontuberculous mycobacteria lung disease in people with cystic fibrosis. Until such evidence becomes available, it is reasonable for clinicians to follow published clinical practice guidelines for the diagnosis and treatment of nodular or bronchiectatic pulmonary disease due to *Mycobacterium avium* complex or *Mycobacterium abscessus* in patients with cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Antibiotic treatment for nontuberculous mycobacteria in people with cystic fibrosis

Nontuberculous mycobacteria are bacteria that are in the same family as tuberculosis and are commonly found in the soil and water. These bacteria can be found in the lungs of people with cystic fibrosis and can cause their lung function to worsen. Although there are guidelines on which antibiotics to use to treat lung infection due to these bacteria, these recommendations are not specific for people with cystic fibrosis. It is also not clear which are the most effective antibiotics. The main purpose of this review was to determine whether treatment with different antibiotic combinations for nontuberculous mycobacterial infection would improve lung function or decrease the frequency of chest infections in people with cystic fibrosis. We found one randomized controlled trial but it included both people with and without cystic fibrosis and we could not get the information specifically about individuals with cystic fibrosis so could not include the information in this review. Until the time when such information is available, clinicians should follow the current guidelines for the diagnosis and treatment of lung infections due to nontuberculous mycobacteria in the general population.

Review question

We reviewed the evidence about using antibiotics to treat nontuberculous mycobacteria infection in people with cystic fibrosis.

Background

Nontuberculous mycobacteria are bacteria that are from the same family as tuberculosis and are commonly found in the soil and water. These bacteria can be found in the lungs of people with cystic fibrosis and may cause their lung function to worsen. Although there are guidelines on which antibiotics to use to treat lung infection due to these bacteria, these recommendations are not specifically for people with cystic fibrosis. It is also not clear which antibiotics work best. The main aim of this review was to show whether or not treating nontuberculous mycobacterial infection with different combinations of antibiotics improves lung function or decreases the frequency of chest infections in people with cystic fibrosis.

Search date

The evidence is current to: 02 September 2016.

Study characteristics

We found one randomized controlled trial but it included both people with and without cystic fibrosis and we could not get the information specifically about individuals with cystic fibrosis so could not include the information in this review.

Key results

Until the time when randomized controlled trial data is available for individuals with cystic fibrosis, clinicians should follow the current guidelines for the diagnosis and treatment of lung infections due to nontuberculous mycobacteria in the general population.

BACKGROUND

Description of the condition

Although cystic fibrosis (CF) is the most common life-shortening genetic disease in the Caucasian population, there has been a dramatic improvement in the median survival age of individuals with CF over the past several decades (CF Foundation 2013; CF Canada 2014; Gibson 2003). As people with CF live longer, they are more likely to become colonized with environmental organisms such as nontuberculous mycobacteria (NTM).

NTM are mycobacteria other than those in the *Mycobacterium tuberculosis* (*M tuberculosis*) complex, which includes *M tuberculosis (* Mandell 2010). They are commonly found in the environment and have been isolated from soil, water, animals, plants and birds (Falkinham 2001). Species of NTM can cause disease, such as lymphadenitis and bronchopulmonary infection, in both immunocompromised as well as immunocompetent people (Mandell 2010).

In the 1990s, NTM species began to be regularly cultured from the respiratory tract of individuals with CF around the world. Original studies by Olivier estimated the prevalence of NTM isolation from individuals with CF to be approximately 13% in the United States of America (Olivier 2003). The majority of NTM species isolated in this study were *Mycobacterium avium* (*M avium*) complex followed by *Mycobacterium abscessus* (*M abscessus*). Subsequent studies have indicated that the prevalence of NTM isolation in the CF population ranges from 5% to 40% (Esther 2005; Fauroux 1997; Levy 2008; Olivier 2003; Sermet-Gaudelus 2003; Campos-Herrero 2016). Depending on the study and patient population, either *M abscessus* complex or *M avium* complex are the most common NTM species isolated. The *M avium* complex consists of *M avium* and *M intracellulare* (Mandell 2010) and the *M abscessus* complex is generally accepted to consist of *M abscessus*, *M bolletii* and *M massiliense* (Blauwendraat 2012; Tortoli 2016). People with CF who have *M avium* complex tend to be older, have better lung function, have a higher rate of *Staphylococcus aureus* (*S aureus)* and a lower rate of *Pseudomonas aeruginosa* (*P aeruginosa*) infection, suggesting a healthy survivorship effect in colonized individuals (Olivier 2003; Roux 2009). In contrast, *M abscessus* infection is more prevalent than *M avium* complex in children with CF and may lead to more deleterious clinical outcomes (Catherinot 2013; Esther 2005; Pierre-Audigier 2005; Qvist 2015). Additional factors such as geographical location and microbiological processing methods may also impact the epidemiology of NTM in people with CF. Specific decontamination procedures in the processing of CF sputum have been recommended to improve the recovery of NTM on culture and the optimal decontamination method may be different for sputum from children compared to sputum from adults (Radhakrishnan 2009; Whittier 1993). As NTM are environmental organisms, certain regions such as the mid-Atlantic and southeastern United States of America are known to have high incidence of mycobacterial disease which has been linked to the high prevalence of NTM in the soil (Brooks 1984; Satyanarayana 2011). Outbreaks of NTM pulmonary disease have also been described in CF populations in tropical regions such as Hawaii (United States) (Johnston 2016).

The presence of NTM species in the respiratory tract of people with CF signifies NTM infection, but NTM pulmonary disease causing clinical deterioration is more difficult to define in a progressive lung disease such as CF. The American Thoracic Society (ATS) in collaboration with the Infectious Diseases Society of America (IDSA) has outlined microbiological, clinical and radiological criteria for NTM disease (Griffith 2007). When examining the effects of NTM infection on the progression of CF lung disease, evidence suggests that CF cases that meet the ATS definition of NTM disease are more likely to show progression of findings on computed tomography of the chest and have a greater decline in lung function, particularly among children (Esther 2005; Griffith 2007; Olivier 2003). In addition, infection with the *M abscessus* species, in contrast to infection with the *M avium* complex, leads to an increased rate of decline in lung function in people with CF compared to those uninfected with NTM, even after controlling for potential confounders (Esther 2010). There is also a report of an outbreak of *M abscessus* complex among individuals with CF in a lung transplant center resulting in 60% mortality (Aitken 2012). Thus, although the distinction between simple infection and disease is often unclear, there are cases of NTM pulmonary disease in people with CF that cause worse clinical outcomes and require antimicrobial treatment.

Description of the intervention

The choice of antibiotics to treat NTM pulmonary infection depends on the species of NTM isolated and is based on data primarily from people who don't have CF. Pulmonary disease caused by *M avium* complex is usually treated with a combination of a macrolide (clarithromycin or azithromycin), rifampin or rifabutin and ethambutol (Griffith 2007). Of the known rapidly growing pathogenic mycobacteria, *M abscessus* is the most resistant to antimicrobials and initial treatment is frequently combination therapy with clarithromycin, amikacin and either cefoxitin or imipenem. Curative therapy of *M abscessus* lung disease is more likely to be achieved with the addition of surgical resection, but this is unlikely to be possible in a diffuse disease such as CF (Griffith 1993). Alternative therapies may be considered if *in vitro* susceptibility testing demonstrates resistance to these initial agents. However, *in vitro* susceptibility results do not always predict *in vivo* clinical response to therapeutic agents as clinical response depends partly on local and host defense systems (Maniu 2001). For *M abscessus* species, there is no correlation between in vitro susceptibility results to any agent and clinical response to the treatment of pulmonary disease by these agents. Nonetheless, alternative classes of antibiotics can be considered if there is a lack of clinical response, concerns for drug toxicity or in vitro resistance noted with initial antimicrobial agents. Based on multiple studies of in vitro antimicrobial susceptibility testing of *M abscessus* isolates, alternative antibiotics include: ciprofloxacin (susceptibility range 3% to 82%); gatifloxacin (7% to 91% susceptible); moxifloxacin (8% to 88% susceptible); linezolid (32% susceptible); and tigecycline (100% susceptible) (Gayathri 2010; Miyasaka 2007; Park 2008; Wallace 2002; Yang 2003). It is important to note that *M abscessus* isolates may be intrinsically resistant to macrolides due to the expression of a novel *erm* gene (Nash 2009). There is some evidence to suggest that clarithromycin induces greater *erm*(41) expression and thus higher macrolide resistance than azithromycin in *M abscessus* infection; both macrolides appear to be equally effective against *M massiliense* species (Choi 2012; Roux 2015). In addition, people with CF may have been previously treated with antibiotics such as ciprofloxacin or azithromycin (for *P aeruginosa*) or linezolid (for methicillin-resistant *S aureus* (MRSA)) (Waters 2012a) and their NTM species may thus already be resistant in vitro to these agents.

How the intervention might work

There are several case reports of people with CF with NTM infection and severe lung disease clinically responding to antimicrobial therapy which targets the specific NTM species leading to eradication of the organism (Fauroux 1997). Antibiotic treatment of NTM pulmonary infections thus has the potential to improve lung function, reduce the frequency of pulmonary exacerbations and eliminate the bacteria from the lung in people with CF. However, there are no data on the effectiveness of early antibiotic therapy to eradicate NTM or chronic antimicrobial suppressive treatment of NTM to prevent lung function decline in CF patients. Early antibiotic therapy to eradicate NTM consists of initiation of antimicrobial treatment on first isolation of an organism in order to eliminate it from the CF lung. Chronic antimicrobial suppressive treatment refers to prolonged antimicrobial therapy to reduce the bacterial burden of the organism in the lung. Furthermore, it is not clear what is the optimal choice of antibiotics or route of antibiotic administration (oral, intravenous or inhaled) with which to treat these patients.

Why it is important to do this review

This review is important because NTM pulmonary infections affect a significant proportion of people with CF worldwide. Data on the treatment and management of these infections is currently extrapolated from a non-CF population and its applicability to CF lung disease is unclear. It is thus necessary to determine whether there are antibiotic treatments for NTM lung infections which result in improved clinical or microbiological outcomes in people with CF.

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

OBJECTIVES

To compare antibiotic treatment to no antibiotic treatment, or to compare different combinations of antibiotic treatment, for NTM lung infections in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adults and children (ages 0 to 18 years) diagnosed with CF (with all levels of disease severity), confirmed with sweat test or genetic testing, or both, who have NTM pulmonary infection (defined as at least two respiratory specimens positive by culture for NTM - post hoc change) will be included. Individuals with a respiratory tract specimen that is positive on stain for acid-fast bacilli (AFB) but culture negative for NTM will not be included. Respiratory tract specimens will include sputum, lung biopsy or bronchoalveolar lavage specimens. Individuals with CF who have received a lung transplant will be excluded.

Types of interventions

The intervention was antibiotics to treat NTM pulmonary infections. We planned to compare NTM antibiotics to no antibiotic treatment as well as compare different NTM antibiotic regimens. Antibiotics included single or multiple antibiotics, oral, inhaled or intravenous antibiotics. Surgical interventions were excluded.

Types of outcome measures

Primary outcomes

1. Lung function
    a. forced expiratory volume in one second (FEV_1) (absolute values litres or per cent (%) predicted or both)
    b. forced vital capacity (FVC) (absolute values litres or % predicted or both)
    c. mid-expiratory flow (FEF_{25-75}) (absolute values litres or % predicted or both)
2. Pulmonary exacerbations, defined as an increase in respiratory symptoms requiring intravenous antibiotic therapy (Fuchs 1994) (if pulmonary exacerbations are not defined in the study, data from that study relating to pulmonary exacerbations will not be reported in this review)
    a. number of pulmonary exacerbations
    b. time between pulmonary exacerbations
    c. time to subsequent exacerbation
3. Adverse events (proportion of participants who had to withdraw or changed therapy)
    a. mild: transient event, no treatment change, e.g. rash, nausea, diarrhoea
    b. moderate: treatment discontinued, e.g. nephrotoxicity, ototoxicity, hepatitis, visual impairment
    c. severe: causing hospitalization or death

Secondary outcomes

1. Quality of life (QoL) (as measured by a validated QoL score, i.e. CFQoL (Gee 2000), CFQ-R (Quittner 2009))
2. Mortality
3. Nutritional parameters
    a. weight
    b. height
    c. body mass index (BMI)
4. Hospitalizations
    a. number of hospitalizations
    b. duration (days)
5. Use of oral antibiotics
6. Quantitative sputum mycobacterial culture (decrease in quantity or eradication) (post hoc change)

Search methods for identification of studies

Electronic searches

We attempted to identify relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: nontuberculous mycobacteria [NTM] AND antibiotics.

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 Cystic Fibrosis and Genetic Disorders Group website.

Date of last search of the CF Trials Register: 02 September 2016.

We also checked the National Institutes of Health (NIH) sponsored website www.clinicaltrials.gov for any ongoing trials (search terms: nontuberculous mycobacteria, atypical mycobacteria, cystic fibrosis) and contacted the authors or manufacturers for potential interim results.

Date of last search of www.clinicaltrials.gov : 03 November 2016.

Searching other resources

We planned to check the reference lists of all trials identified for any further relevant trials.

Data collection and analysis

One completed trial was identified by the searches, but data specific to individuals with CF could not be obtained from the pharmaceutical company so we were unable to carry out the planned analysis as detailed below. However, if in future updates of this review we are able to obtain data from any trials, we plan the following analysis.

Selection of studies

The two authors (VW, FR) will independently apply the inclusion criteria to all potential trials. The authors will not be blinded to the trials. If a disagreement occurs, it will be resolved by discussion with a third person (Nikki Jahnke (NJ)).

Data extraction and management

Using a data collection form, two authors (VW, FR) will independently obtain data from published reports or from trial investigators. If a disagreement occurs, the authors will resolve this by discussion with a third person (NJ). In addition to information about trial references and authors and verification of trial eligibility, the data collection form includes information about the methods of the trial (e.g. trial duration, type of trial, blinding, number of dropouts and potential confounders). When possible, the authors will extract data on sequence generation and allocation concealment. The authors will report characteristics of the trial participants including age, sex and setting of the trial on the form. Furthermore, they will also describe the intervention with regards to type of antibiotic, route of delivery, doses and length of treatment. The authors will initially analyze data from trials with different types of antibiotic, routes of delivery, doses and lengths of treatment all together and then separately in subgroup analyses (e.g. data from trials comparing oral antibiotic NTM treatments - see below). The authors will collect data for all randomized participants and attempt to collect the following data: the mean change (before and after antibiotic therapy) in FEV_1 and FVC, FEF_{25-75}; the mean hospital length of stay; the time to subsequent pulmonary exacerbation; the number of adverse events; the mean QoL score after antibiotic therapy; the number of mortalities and change in weight (before and after antibiotic therapy) (see Types of outcome measures for a complete list of outcomes). For each mean value, the authors will also obtain the standard deviation (SD) (variation from the average). For time to subsequent exacerbation, they will try to obtain log-rank estimates and Cox model estimates.

Given that NTM pulmonary infections are generally treated with more long-term antibiotics, the authors plan to measure outcomes at the following time points: one month and up to six months; six months and up to one year; and one year or longer interval. They will measure the outcome 'Time to subsequent pulmonary exacerbation' in monthly intervals after these time points. The authors will also consider outcomes measured at other time points.

Assessment of risk of bias in included studies

The authors will assess the included trials for the following types of bias: selection bias (bias in choosing study participants); performance bias (bias in the care of study participants); attrition bias (bias in how participant loss to follow up is handled); detection bias (biased assessment of outcome); and reporting bias (bias in the reporting of study outcomes) (Higgins 2011b) using the following strategies as outlined below.

Assessment of generation of allocation sequences

They 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. uncertain risk of bias: if the trial is described as randomised but the method used to generate the allocation sequence is not stated.

Assessment of concealment of allocation sequences

They 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. uncertain 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, the authors 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 study 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 uncertain 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, the authors 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 uncertain risk of bias if the trial does not specify the above outlined information.

Assessment of selective reporting

The authors will review the included trials for selective reporting (Higgins 2011b). They 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, they will review the 'Methods' and 'Results' sections and use their discretion to determine if selective reporting has occurred.

Assessment of other potential sources of bias

The authors 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 study validity in reviews

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

Measures of treatment effect

For dichotomous data, the authors will gather information on participants randomized to each treatment group (antibiotics versus no antibiotics or one antibiotic regimen versus another regimen), based on an intention-to-treat analysis, and the number of events. They plan to include interim results from individual randomized participants with CF from ongoing studies in the analysis. They will define time points for each trial outcome according to when it was measured (one to six months, six months up to one year, one year or over). They will analyze trial outcomes separately according to these time points. The authors plan to pool the treatment effect across studies to determine a relative risk (RR) and its 95% confidence intervals (CIs) for each outcome.

For continuous data, the authors will calculate the difference between the mean (average) values (MD) of treatment effect for each group, the number in each group and the standard deviation (SD). As a summary statistic across trials, they will use the MD if the same scale is used, or the standardised mean difference (SMD) if different scales are used (e.g. QoL measurements) both with 95% CIs. For time-to-event data, most trials use Kaplan-Meier survival analysis. The authors 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 (Deeks 2011; Parmar 1998).

Unit of analysis issues

The authors will include data from cluster-randomized trials if the information is available. For clusterrandomized trials, they will calculate the intra-cluster correlation coefficient (ICC) according to Donner (Donner 2001). They will also include data from cross-over trials if the information is available. Continuous data from cross-over trials will be analyzed using one of three approaches: treat the study 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; impute missing SDs (Higgins 2011c). Cross-over trials with dichotomous outcomes require more complicated analysis methods and for this the authors will consult with a statistician (Elbourne 2002).

Dealing with missing data

Data are often missing for participants who are lost to follow-up. In these situations, the authors will perform an available-case analysis (analyzing data for every participant for whom the outcome is obtained). They will report the percentages of participants from whom no outcome data were obtained on the data collection form. They 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. The authors will consider variation in the degree of missing data across trials as a potential source of heterogeneity.

Assessment of heterogeneity

In performing a meta-analysis, the authors will measure the variability of results between trials (heterogeneity) using the I^2 method (with CIs) outlined by Higgins (Higgins 2003). The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than 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. The authors will consider a value greater than 50% as substantial heterogeneity. They will also visually inspect the forest plot to assess the heterogeneity between trials.

Assessment of reporting biases

To investigate whether the review is subject to publication bias, and if they are able to include sufficient trials (at least 10), the authors will construct a funnel plot. In the absence of bias, the plot should resemble a symmetrical inverted funnel (Sterne 2011). If there is asymmetry, the authors will consider publication bias and other reasons (such as location biases, true heterogeneity, poor methodological quality of smaller trials etc) as a potential cause.

Data synthesis

If the authors consider that the trials are clinically similar enough to combine (e.g. studies comparing different antibiotic combinations to treat pulmonary exacerbations in participants with NTM infection), they will investigate statistical heterogeneity as outlined below. If there is no substantial heterogeneity, they will calculate the pooled effect estimates using a fixed-effect model. If they identify substantial heterogeneity (I^2 statistic is greater than 50%), they will perform a random-effects meta-analysis to incorporate heterogeneity between trials.

Subgroup analysis and investigation of heterogeneity

If the authors find substantial heterogeneity (I^2 statistic is greater than 50%) (Higgins 2003), they will explore the potential causes of this (i.e. different types of antimicrobial treatment such as oral, inhaled or intravenous; different participant populations; different species of NTM etc) and if possible (if at least five trials are included for that outcome) conduct subgroup analyses of the trials. For example, trial results may vary if different types of antibiotic treatment are used (e.g. oral, inhaled or intravenous) for the treatment of pulmonary infection, or different treatment durations (e.g. six months versus one year). There may also be differences depending on whether antibiotics are used to treat a first-time infection (eradication) versus an established, chronic infection (when more than 50% of cultures are positive in the previous 12 months). Finally, there may be differing effects of antibiotic treatment of NTM pulmonary infection depending on the type of NTM species isolated (e.g. antimicrobial treatment of *M abscessus* pulmonary infections may show more of a clinical benefit than treatment of *M avium* complex infections).

Sensitivity analysis

If the authors are able to include at least 10 trials in the review, they will perform a sensitivity analysis to determine whether the conclusions are robust to decisions made during the review process such as inclusion or exclusion of particular studies from a meta-analysis, imputing missing data or choice of a method for analysis. They will investigate whether changing which studies are included, based on their assessment of the risk of bias (initially including all trials and then excluding any with a high risk of bias) or changing our chosen statistical model (i.e. random-effects model compared to a fixed-effect model) changes the results of the review. If the sensitivity analyses do not significantly change the results presented in the review, it strengthens the confidence that can be placed in these results. The authors will present the results in an influence plot, as appropriate.

RESULTS

Description of studies

We have identified one randomized controlled trial which has been completed but it included both individuals with and without CF (Olivier 2016). We have contacted the trial investigators and the pharmaceutical company who sponsored the trial (Insmed), but to date they have declined to provide any data specific to individuals with CF. For this reason, we currently list this trial as 'Awaiting classification' and we will assess it for inclusion if the data specific to individuals with CF becomes available.

This phase 2, randomized, double-blind controlled trial included adults (both with and without CF) who met criteria for pulmonary non-tuberculous mycobacterial disease defined by the ATS and the IDSA. Participants had received ongoing multi-drug treatment (based on ATS and IDSA guidelines) for at least six months prior to screening and had persistently positive cultures for *M avium* complex or *M abscessus*. Participants were randomized 1:1 to either liposomal amikacin for inhalation at a dose of 590 mg or placebo (empty liposomes) once daily via the PARI Investigational eFlow® Nebulizer; this regimen was added to their ongoing stable multi-drug regimen for 84 days. At the end of this period, participants could consent to receive open-label treatment with daily liposomal amikacin inhaled and their background regimen for an additional 84 days. The primary endpoint was the change from baseline to day 84 on a semi-quantitative mycobacterial growth scale. Other endpoints included sputum conversion, 6-minute walk distance and adverse events. The modified intent-to-treat population included 89 participants (liposomal amikacin for inhalation n = 44; placebo n = 45); 19% of participants had CF, 64% had predominantly *M avium* complex infection and 36% had predominantly *M abscessus* infection.

Risk of bias in included studies

No trials have yet been included in this review.

Effects of interventions

No trials have yet been included in this review.

DISCUSSION

Summary of main results

There were no data from randomized controlled trials of treatment of nontuberculous mycobacteria (NTM) pulmonary infection in people with cystic fibrosis (CF) which could be included in this review. One trial has been listed as 'Awaiting assessment' until we are able to obtain CF-specific data from the trial sponsor (Insmed) (Olivier 2016).

This trial of liposomal amikacin for inhalation in adults (19% of whom had CF) who met defined criteria for pulmonary NTM disease, had received ongoing multi-drug treatment for at least six months and had persistently positive cultures for *Mycobacterium avium* (*M avium*) complex or *Mycobacterium abscessus* (*M abscessus*) (Olivier 2016). In addition to their ongoing multi-drug regimen, participants were randomized to inhaled liposomal amikacin or placebo for 84 days. Although the primary endpoint of a reduction in semi-quantitative mycobacterial growth was not achieved, a greater proportion of participants in the liposomal amikacin group (32%) demonstrated sputum conversion (at least one negative mycobacterial sputum culture) than in the placebo group (9%) ($P = 0.006$); however, most of those in whom sputum conversion was observed did not have CF and were infected with *M avium* complex rather than *M abscessus* infection. Those in the liposomal amikacin group also had a greater improvement in the 6-minute walk test at day 84 ($P = 0.017$).

Overall completeness and applicability of evidence

The only identified randomized controlled trial to date was in adults only (Olivier 2016). To date, we do not have access to the data for those participants with CF, it is therefore not possible to determine the relevance of these findings to the CF population.

Agreements and disagreements with other studies or reviews

Traditionally, antimicrobial therapy of NTM lung infection (including in people with CF) has been guided by protocols summarized in the statement endorsed by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) (Griffith 2007).

Most data are available for *M avium* complex and these recommendations are based on evidence with a highest grade of II (evidence from at least one well-designed clinical trial without randomization). The initial controlled-treatment studies were undertaken using only first-line anti-tuberculosis (TB) drugs, which have 10 to 100 times less in vitro activity against *M avium* complex than against *Mycobacterium tuberculosis* (*M tuberculosis*). The Research Committee of the British Thoracic Society conducted the first randomized controlled trial of 75 participants with *M avium* complex pulmonary disease. Participants were randomized to two years of either rifampicin and ethambutol or to rifampicin, ethambutol and isoniazid (British Thoracic Society 2001; British Thoracic Society 2002). Although two thirds of enrolled participants had co-existing lung disease, it was not specified if any of them had CF. In this trial, there were fewer treatment failures or relapses with the rifampicin, ethambutol and isoniazid regimen compared to the rifampicin and ethambutol regimen (16% versus 41% respectively, P = 0.033). However, there was a suggestion that the rifampicin, ethambutol and isoniazid regimen was associated with higher death rates overall. The advent of the newer macrolides, clarithromycin and azithromycin, was a significant advancement in the treatment of pulmonary disease due to *M avium* complex, as these drugs have good in vitro and clinical activity against *M avium* complex (Griffith 2007). Clinical studies of macrolide use with traditional anti-TB drugs have shown superior sputum conversion rates compared to historical controls (Griffith 1996; Wallace 1994; Wallace 1996). However, in a recent two-year trial of mycobacterial lung disease, clarithromycin was compared to ciprofloxacin as alternative third drugs to be added to rifampicin and ethambutol and did not demonstrate any superiority in terms of clinical outcomes in people infected with *M avium* complex (Jenkins 2008).

The other NTM species commonly isolated from the respiratory tract of people with CF is *M abscessus*. In contrast to *M avium* complex, *M abscessus* is uniformly resistant to the standard anti-tuberculous agents (Griffith 2007). There are few comparative trials of differing antimicrobial interventions for the treatment of pulmonary NTM disease due to *M abscessus.* Our search identified only one randomized, placebo-controlled trial testing liposomal amikacin for inhalation (Olivier 2016). Liposomal amikacin is an aminoglycoside drug that has been enveloped in a spherical phospholipid bilayer known as a liposome. This formulation of the drug can be delivered via inhalation to the lower airways where the lipid bilayer fuses with the bacterial cell membrane, allowing delivery of the drug into the cell (Beaulac 1997; Sachetelli 2000). The trial did not achieve its primary endpoint (reduction in semi-quantitative mycobacterial growth), but showed sputum conversion (at least one negative mycobacterial sputum culture) (P=0.006) and improvement in 6-minute walk test (P=0.017) at day 84 in the liposomal amikacin group compared to the placebo group. Unfortunately most participants in whom sputum conversion was observed did not have CF and were infected with *M avium* complex rather than *M abscessus* infection.

AUTHORS' CONCLUSIONS

Implications for practice

This review did not find any evidence from randomized controlled trials of the effectiveness of different antimicrobial treatment for NTM lung disease in people with CF. Until such evidence becomes available, it is reasonable for clinicians to follow clinical practice guidelines for the management of NTM pulmonary infections in individuals with CF. The Cystic Fibrosis Foundation and the European Cystic Fibrosis Society have recently issued a consensus guideline for the screening, investigation, diagnosis and treatment of individuals with CF and NTM pulmonary disease due to *M avium* complex or *M abscessus* (Floto 2016). The antibiotic treatment regimens are generally complex due to the long treatment durations and high frequency of associated side effects; consultation with specialists in the field is generally recommended.

Implications for research

Given the high prevalence of NTM pulmonary infection in certain CF centers and the concern of adverse effect of *M abscessus* on lung function in young children, properly-designed and adequately-powered randomized controlled trials are needed to determine if antibiotic treatment of NTM species improves clinical outcomes, such as forced expiratory volume in one second (FEV_1), in people with CF. However, properly conducted randomized controlled interventional trials are difficult to undertake in this population as there are many potential confounding variables that can affect lung function. In addition, these trials may require large sample sizes to detect significant changes in FEV_1. Prospective observational studies of the diagnosis (PREDICT Trial (NCT02073409)) and algorithms for the treatment (PATIENCE Trial (NCT02419989)) of NTM infections in CF are also being conducted with outcome measures including microbiologial eradication, lung function and nutritional status changes and frequency of pulmonary exacerbations. Although not randomized controlled trials, such data may help guide the future management of individuals with CF with this type of infection.

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CHARACTERISTICS OF STUDIES

Characteristics of studies awaiting assessment *[ordered by study ID]*

Olivier 2016

Methods	Randomized (1:1), double-blind, placebo-controlled trial. Participants to visit the clinic approximately every 28 days for efficacy, safety and tolerability evaluations.

Olivier 2016 *(Continued)*

Participants	Adults (both with CF and without CF) with recalcitrant non-tuberculous mycobacterial lung disease on a stable multi-drug regimen. Eligible age range 18 to 75 years. Estimated number to recruit: 100.
Interventions	Liposomal amikacin (Arikace®, 560 mg) for inhalation once daily using the PARI Investigational eFlow® Nebulizer (administration time approximately 13 minutes) or placebo (administration procedures, volume and administration time is the same as for Arikace®). Randomized treatment period planned for 84 days (Arikace® and placebo) with an option for 84 additional days of dosing with Arikace® in the open-label extension.
Outcomes	Primary outcome • Change in semi-quantitative mycobacterial culture results from baseline to end of treatment Secondary outcomes • Proportion of participants with culture conversion to negative • Time to 'rescue' anti-mycobacterial drugs • Change from baseline in 6-minute walk distance and oxygen saturation • Change from baseline in patient-reported outcomes • Evaluation of safety and tolerability
Notes	Principle investigator confirmed inclusion of participants with CF. Supported by Insmed Incorporated.

CF: cystic fibrosis

WHAT'S NEW

Date	Event	Description
15 December 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register identified four new references to a trial previously listed as 'ongoing'; this trial is now listed as 'Awaiting classification' until we are able to obtain the data specifically relating to the participants with cystic fibrosis (Olivier 2016).
15 December 2016	New citation required but conclusions have not changed	Since no new data have been added to the review, our conclusions have not changed.

HISTORY

Protocol first published: Issue 7, 2012
Review first published: Issue 12, 2012

Date	Event	Description
3 December 2014	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified one additional reference to the trial listed in 'Studies awaiting classification' (Olivier 2016).
3 December 2014	New citation required but conclusions have not changed	No new references have been added to this update, therefore our conclusions remain the same.

CONTRIBUTIONS OF AUTHORS

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

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. Definition of NTM infection

In the protocol NTM infection was defined as "at least one respiratory specimen", this has been changed to the current definition which is the standard definition by the ATS of "at least two respiratory specimens positive by culture for NTM".

2. Secondary outcome measures

A sixth secondary outcome has been added "Quantitative sputum mycobacterial culture". This outcome was included in the original draft of the protocol, but removed following the advice of one of the peer reviewers and the contact editor. When the review authors looked at past and current ongoing RCTs for NTM lung disease, it became apparent that this is one of the main outcomes which is usually assessed and for the CF population (who may not be expected to convert their sputum), may be the most relevant. Hence the outcome has been listed again.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Cystic Fibrosis [*microbiology]; Drug Therapy, Combination [methods]; Lung Diseases [*drug therapy] [microbiology]; Mycobacterium Infections, Nontuberculous [*drug therapy]; Nontuberculous Mycobacteria

MeSH check words

Humans