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Antibiotic therapy for chronic infection with *Burkholderia cepacia* complex in people with cystic fibrosis (Review)

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[Intervention Review]

Antibiotic therapy for chronic infection with *Burkholderia cepacia* complex in people with cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis (CF) a life-limiting inherited disease affecting a number of organs, but classically associated with chronic lung infection and progressive loss of lung function. Chronic infection by *Burkholderia cepacia* complex (BCC) is associated with increased morbidity and mortality and therefore represents a significant challenge to clinicians treating people with CF. This review examines the current evidence for long-term antibiotic therapy in people with CF and chronic BCC infection.

Objectives

The objective of this review is to assess the effects of long-term oral and inhaled antibiotic therapy targeted against chronic BCC lung infections in people with CF. The primary objective is to assess the efficacy of treatments in terms of improvements in lung function and reductions in exacerbation rate. Secondary objectives include quantifying adverse events, mortality and changes in quality of life associated with treatment.

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 online trial registries and the reference lists of relevant articles and reviews.

Date of last search: 12 April 2021.

Selection criteria

Randomised controlled trials (RCTs) of long-term antibiotic therapy in people with CF and chronic BCC infection.

Data collection and analysis

Two authors independently extracted data, assessed risk of bias and assessed the quality of the evidence using GRADE.

Main results

We included one RCT (100 participants) which lasted 52 weeks comparing continuous inhaled aztreonam lysine (AZLI) and placebo in a double-blind RCT for 24 weeks, followed by a 24-week open-label extension and a four-week follow-up period. The average participant age was 26.3 years, 61% were male and average lung function was 56.5% predicted.

Treatment with AZLI for 24 weeks was not associated with improvement in forced expiratory volume in one second (FEV₁), mean difference 0.91% (95% confidence interval (CI) -3.15 to 4.97) (moderate-quality evidence). The median time to the next exacerbation was 75 days in

the AZLI group compared to 51 days in the placebo group, but the difference was not significant ($P = 0.27$) (moderate-quality evidence). Similarly, the number of participants hospitalised for respiratory exacerbations showed no difference between groups, risk ratio (RR) 0.88 (95% CI 0.53 to 1.45) (moderate-quality evidence). Overall adverse events were similar between groups, RR 1.08 (95% CI 0.98 to 1.19) (moderate-quality evidence). There were no significant differences between treatment groups in relation to mortality (moderate-quality evidence), quality of life or sputum density.

In relation to methodological quality, the overall risk of bias in the study was assessed to be unclear to low risk.

Authors' conclusions

We found insufficient evidence from the literature to determine an effective strategy for antibiotic therapy for treating chronic BCC infection.

PLAIN LANGUAGE SUMMARY

Antibiotic treatments for long-term *Burkholderia cepacia* infections in people with cystic fibrosis

Review question

We reviewed the evidence for long-term antibiotic treatments for people with cystic fibrosis who are infected with *Burkholderia cepacia* complex (bacteria composed of at least 20 different species).

Background

People with cystic fibrosis often suffer from repeated chest infections and eventually their lungs become permanently infected by bacteria, such as a family of bacteria called *Burkholderia cepacia* complex which can cause problems because many antibiotics do not work against them and they can cause a quicker deterioration in lung disease. We wanted to discover whether using long-term antibiotic treatment was beneficial for people with cystic fibrosis and *Burkholderia cepacia* complex infection.

Search date

The evidence is current to: 12 April 2021.

Study characteristics

This review included one study of 100 people aged between 6 and 57 years old. The study compared an inhaled antibiotic called aztreonam to placebo (a substance which contains no medication) and people were selected for one treatment or the other randomly (by chance). The study lasted 52 weeks.

Key results

The only study included in this review found inhaled aztreonam had no beneficial effect on lung function or rates of chest infections in people with cystic fibrosis and *Burkholderia cepacia* complex infection. There was no difference between groups in relation to the average time to the next exacerbation or the number of people hospitalised for an exacerbation. Overall adverse events were similar between groups and with regards to other outcomes assessed, there was no difference between treatment groups for mortality, quality of life or sputum density. More research is needed to establish if other inhaled antibiotics may be useful.

Quality of the evidence

Overall quality of evidence was considered to be moderate across all outcomes, which means further research is likely to have an important impact on results.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings - AZLI compared with placebo for chronic *Burkholderia cepacia* complex infection in people with CF

AZLI compared with placebo for chronic *Burkholderia cepacia* complex infection in people with CF

Patient or population: adults and children with CF

Settings: CF treatment centres across North America

Intervention: AZLI for inhalation 75 mg three times a day via nebuliser for 24 weeks

Comparison: placebo, three times a day via nebuliser for 24 weeks

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	AZLI				
Relative change in FEV ₁ % predicted	The mean change in FEV ₁ (% predicted) in the control group was -0.75%	The mean change in FEV ₁ (% predicted) in the intervention group was 0.91% higher (3.15% lower to 4.97% higher)	NA	99 (1 study)	⊕⊕⊕⊖ Moderate^a	
Days to next exacerbation	See comment		NA	100 (1 study)	⊕⊕⊕⊖ Moderate^a	Median days to next exacerbation in the control group was 75 days. Median days to next exacerbation in the intervention group was 24 days lower.
Participants hospitalised for respiratory exacerbation	400 per 1000	352 per 1000 (212 to 580)	RR 0.88 (95% CI 0.53 to 1.45)	100 (1 study)	⊕⊕⊕⊖ Moderate^a	
Any AEs	904 per 1000	976 per 1000 (886 to 1076)	RR 1.08 (95% CI 0.98 to 1.19)	100 (1 study)	⊕⊕⊕⊖ Moderate^a	Wheeze was more frequent in the AZLI group compared to placebo but groups were otherwise well matched.
Mortality	There were 0 deaths in the placebo group	There were 2 deaths in the intervention arm	RR 5.41 (95% CI 0.27 to 109.87)	100 (1 study)	⊕⊕⊕⊖ Moderate^a	

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

AE: adverse event; **AZLI:** aztreonam lysine for inhalation; **CF:** cystic fibrosis; **CI:** confidence interval; **FEV₁:** forced expiratory volume in one second; **RR:** risk ratio.

GRADE Working Group grades of evidence

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

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

Low certainty: 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 certainty: we are very uncertain about the estimate

a Downgraded once due to imprecision of results (small sample size and subsequent wide CIs)

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is a life-threatening inherited disease affecting over 10,000 people in the UK, 35,000 in Europe and 30,000 in the USA (CFF 2016; CF Trust 2017; Farrell 2008). There have been significant improvements in CF survival since the 1930s when 70% of those with CF died in infancy, to a current median predicted survival of 43.5 years (CF Trust 2017). Early CF deaths are now rare: over 95% of children with CF enter adulthood and recent predictions are that by 2025, the number of CF adults in Europe will have nearly doubled (Burgel 2015).

In CF, the genetic autosomal-recessive defect in the CFTR protein causes abnormal salt and water movements across mucus-producing cell surfaces. This results in thick mucus leading to a combination of infection and inflammation with subsequent local organ damage, which is most apparent in the lungs and pancreas, but affects many other organs. In the lungs the hallmarks of disease are chronic airway inflammation and chronic infection with difficult to treat pathogens, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Burkholderia cepacia* complex (BCC). Chronic airway infection is associated with a progressive loss of lung function, which is the primary cause of death in people with CF (Corey 1997).

BCC is comprised of a group of over 20 closely related species with a cumulative annual prevalence in people with CF of 3% to 5%; *Burkholderia cenocepacia* and *Burkholderia multivorans* account for 85% to 97% of BCC infections (CFF 2016; CF Trust 2017; Drevinek 2010; Mahenthiralingam 2002; Vandamme 2011). These two pathogens are associated with poor outcomes including accelerated pulmonary decline, a necrotizing pneumonia known as 'cepacia syndrome' and a higher mortality rate (Aris 2001; Mahenthiralingam 2002; Zlosnik 2015). *B. cenocepacia* is the more pathogenic of the two, with an increased likelihood of chronic infection and reduced survival compared to *B. multivorans* (Jones 2004; Mahenthiralingam 2001). Acquisition is often from environmental sources, but clonal transmission of epidemic strains has been extensively reported, particularly for *B. cenocepacia*, and hence infection control and segregation measures are required to prevent cross-infection (Ledson 1998; LiPuma 2010; Zlosnik 2015).

Resistance to aminoglycosides, to most beta-lactams as well as to polymyxins is common within BCC and some species have the ability to develop resistance to any agent resulting in pan-resistant strains (CF Trust 2017; Drevinek 2010; Mahenthiralingam 2002). Therefore, the clinical management of chronic BCC infection in CF poses a challenge to clinicians.

Description of the intervention

Long-term antibiotics are one of the mainstays of treatment in people with CF with chronic infection, these are usually inhaled or given orally to reduce the bacterial burden in sputum. Inhaled antibiotics allow rapid deposition of high concentrations of antibiotics direct to the site of action and hence represent an attractive strategy. In those with *P. aeruginosa* infection, colistimethate, tobramycin and aztreonam have all demonstrated clinical benefit (Gibson 2003; McCoy 2008; Retsch-Bogart 2008; Ryan 2011). The low systemic absorption associated with inhaled antibiotics can help avoid some of the side-effects seen with

intravenous antibiotics used in acute infection (Weber 1995). Oral antibiotics are quick and convenient to take, but may not be able to deliver as high a concentration to the lung as inhaled formulations. Nevertheless, oral macrolide therapy has been shown to be effective in CF with a recent Cochrane Review demonstrating a reduction in pulmonary exacerbations and improved respiratory function after six months treatment of azithromycin (Southern 2012).

How the intervention might work

Long-term antibiotic therapy targeted towards *P. aeruginosa* infections has been associated with improved clinical outcomes in people with CF and both inhaled and oral antibiotic therapies are recommended in that cohort (NICE 2017). There is no clear guidance on whether treatments targeted towards BCC are effective, but inhaled antibiotics may theoretically overcome traditional resistance breakpoints due the 100-fold increase in concentrations achieved in the lung. Hence antimicrobial agents, with little or no activity against BCC at systemically achievable concentrations, may still exert bactericidal effects when inhaled into the lungs (Ramsey 1999).

Furthermore, macrolides have no in vitro bactericidal effect against *P. aeruginosa*, yet appear to produce marked clinical improvements. This is most likely secondary to an anti-inflammatory effect with attenuated cytokine production and reductions in neutrophil elastase reported in a number of studies (Bell 2005; Wales 1999).

Hence, despite BCC often demonstrating in vitro resistance to many of the antimicrobial agents available for chronic use in CF, there is hope that the principles of treatment and agents used in chronic *P. aeruginosa* infection are relevant in BCC infection.

Why it is important to do this review

Chronic infection with BCC is associated with poorer clinical outcomes in people with CF. The inherent antibiotic resistance in these species makes the treatment of chronic infection challenging for clinicians. This review aims to assess the current evidence with regards to antibiotic treatment options for people with CF who are chronically infected with BCC to identify evidence-based strategies.

Strategies will primarily be assessed in terms of their ability to preserve or improve pulmonary function and to reduce acute pulmonary exacerbations.

OBJECTIVES

The objective of this review is to assess the effects of long-term oral and inhaled antibiotic therapy targeted against chronic BCC lung infections in people with CF. The primary objective is to assess the efficacy of treatments in terms of improvements in lung function and reductions in exacerbation rate. Secondary objectives include quantifying adverse events, mortality and changes in quality of life (QoL) associated with treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including those with a cross-over design, were considered for inclusion in this review.

Types of participants

Adults and children with CF (confirmed by either a positive sweat test or the identification of two pathogenic CFTR mutations) and chronic BCC infection (defined as a positive respiratory culture growth of BCC within the last six months and BCC growth in more than 50% of all respiratory cultures in the last 12 months) (Lee 2003).

Types of interventions

Long-term (defined as a period of eight weeks or more) antibiotics (all agents, doses and regimens) via either the inhaled or oral route. Studies were included if there was comparison to either no treatment, placebo, another antibiotic agent, another mode of delivery, or another dose or regimen of the same antibiotic.

Types of outcome measures

We assessed the following outcomes.

Primary outcomes

1. Lung function
 - a. forced expiratory volume in one second (FEV₁)
 - i. absolute change in volumes, % predicted or both
 - ii. relative change in volumes, % predicted or both
2. Pulmonary exacerbations
 - a. time to next exacerbation
 - b. hospitalisations
 - c. exacerbation rate
 - d. IV antibiotic use
3. Adverse events
 - 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 hospitalisation or death

Secondary outcomes

1. Mortality
2. QoL
 - a. validated QoL score, e.g. CFQ-R Respiratory Symptom Score (RSS)
3. BCC culture
 - a. sputum density of BCC
4. Changes in inflammatory markers
 - a. sputum or bronchoalveolar lavage (BAL) samples
 - b. serum or blood

Search methods for identification of studies

We searched for all relevant published and unpublished studies without restrictions on language, year or publication status.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist conducted a systematic search of the Group's Cystic Fibrosis Trials Register for relevant trials using the following terms: *Burkholderia cepacia*:kw OR mixed infections:kw.

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 through 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 the most recent search of the Group's Cystic Fibrosis Trials Register: 12 April 2021.

We searched the following trials registries:

- the World Health Organization (WHO) International Clinical Trials Registry Platform (www.who.int/trialsearch) (searched 22 October 2021);
- Clinicaltrials.gov (www.clinicaltrials.gov) (searched 22 October 2021).

See an appendix for details of the searches ([Appendix 1](#)).

Searching other resources

We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant studies.

Data collection and analysis

Selection of studies

Two review authors (FF, DN) independently selected studies to be included in the review. Where there was disagreement on the suitability of a study for inclusion, all three review authors reached a consensus decision after discussion.

Data extraction and management

Each author independently extracted data using standardised data collection forms. We planned to compare outcome measures at eight weeks to three months, over three months to six months and over six months to one year. However, we planned that should we identify studies with outcome data at alternative time-points, we would also consider these. We planned to analyse oral and inhaled antibiotics separately, however, we found no relevant studies of oral antibiotics.

Assessment of risk of bias in included studies

Each review author independently assessed studies following the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Briefly, a judgement of 'low risk', 'high risk' or 'unclear risk' of bias was made for each of the seven domains in the Cochrane tool which are listed below.

- Random sequence generation
- Allocation concealment
- Blinding of participant personnel
- Blinding of outcome assessment

- Incomplete outcome data
- Selective reporting
- Other sources of bias

In the case of any disagreements between the three review authors, we aimed to reach a consensus by discussion.

Measures of treatment effect

For continuous outcomes, such as change in lung function we calculated the mean difference (MD) with corresponding 95% confidence intervals (CI) to measure treatment effect. If there had been more than one study included, which reported multiple variations of a similar outcome, we planned to calculate the standardized mean difference (SMD) and corresponding 95% CIs.

For dichotomous outcomes such as mortality, we calculated risk ratios (RR) and corresponding CIs.

For the included studies, where SEs were reported (e.g. relative change for FEV₁% predicted), in order to enter the data into 'Data and analyses' we calculated the SD using the formula: $SD = SE \times \text{square root of } n$.

Unit of analysis issues

No cross-over studies were included in the review. In future updates of this review, should cross-over studies be included we plan to include data from cross-over studies should the duration of treatment meet the inclusion criteria and if the relevant information, as described by Elbourne is available (Elbourne 2002). In such cases we plan to treat the studies as parallel studies and pool the intervention arms to be compared against the control arms, or alternatively perform analysis on the first period only, depending on the information available.

Dealing with missing data

We assessed for missing data in reported results and report the percentage of participants from whom no outcome data were obtained on the data collection form. Unless there is reason to suspect data are not missing at random, we included data on only those whose results are known in the analysis and use the total participants with complete data as the denominator rather than the total number of participants (Higgins 2011b).

Assessment of heterogeneity

There were insufficient studies to assess heterogeneity, however should more studies be conducted in the future we plan to assess heterogeneity of inconsistencies across studies using the I^2 statistic and interpret the I^2 statistic based on the thresholds of heterogeneity set out by Higgins (Higgins 2003):

- 0% to 40%: might not be important;
- 30% to 60%: may represent evidence of moderate heterogeneity;
- 50% to 90%: may represent evidence of substantial heterogeneity;
- 75% to 100%: may represent evidence of considerable heterogeneity.

Assessment of reporting biases

If we are able to include more studies in the future, we will attempt to assess whether our review is subject to publication bias by using a funnel plot; if we detect asymmetry, we will explore causes other than publication bias.

Data synthesis

When sufficient data are available we plan to assess whether studies are clinically similar enough to combine into meta-analyses, and if so, we will assess for heterogeneity as outlined above. If we identify at least substantial heterogeneity (higher than 50%), we will use a random-effects model, otherwise, we will use a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We planned to conduct a subgroup analysis on species (*B. cenocepacia* and *B. multivorans*), however, we were unable to do so due to lack of studies and data. In future updates of this review, when possible, we plan to consider the potential effects of the intermittent use of acute antibiotics by undertaking a subgroup analysis.

Sensitivity analysis

If there are sufficient studies in future updates of this review (10 or more) we will review the validity of our conclusions by carrying out sensitivity analyses to assess the influence of a high risk of bias (any domain) on our results and conclusions and the effects of a fixed-effect analysis versus a random-effects analysis. This has not been possible to date due to a lack of eligible studies.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table for the included comparison. We included reported changes in the primary outcomes FEV₁ (changes in relative % predicted or volumes or both), time to next exacerbation and hospitalisations, mortality and adverse events (mild, moderate and severe). We listed population, setting, intervention and comparison and reported an illustrative risk for the experimental and control intervention with MDs re-expressed as RRs as required (Schünemann 2011b). The grade of certainty for each outcome was adjudicated as moderate using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Schunemann 2006).

RESULTS

Description of studies

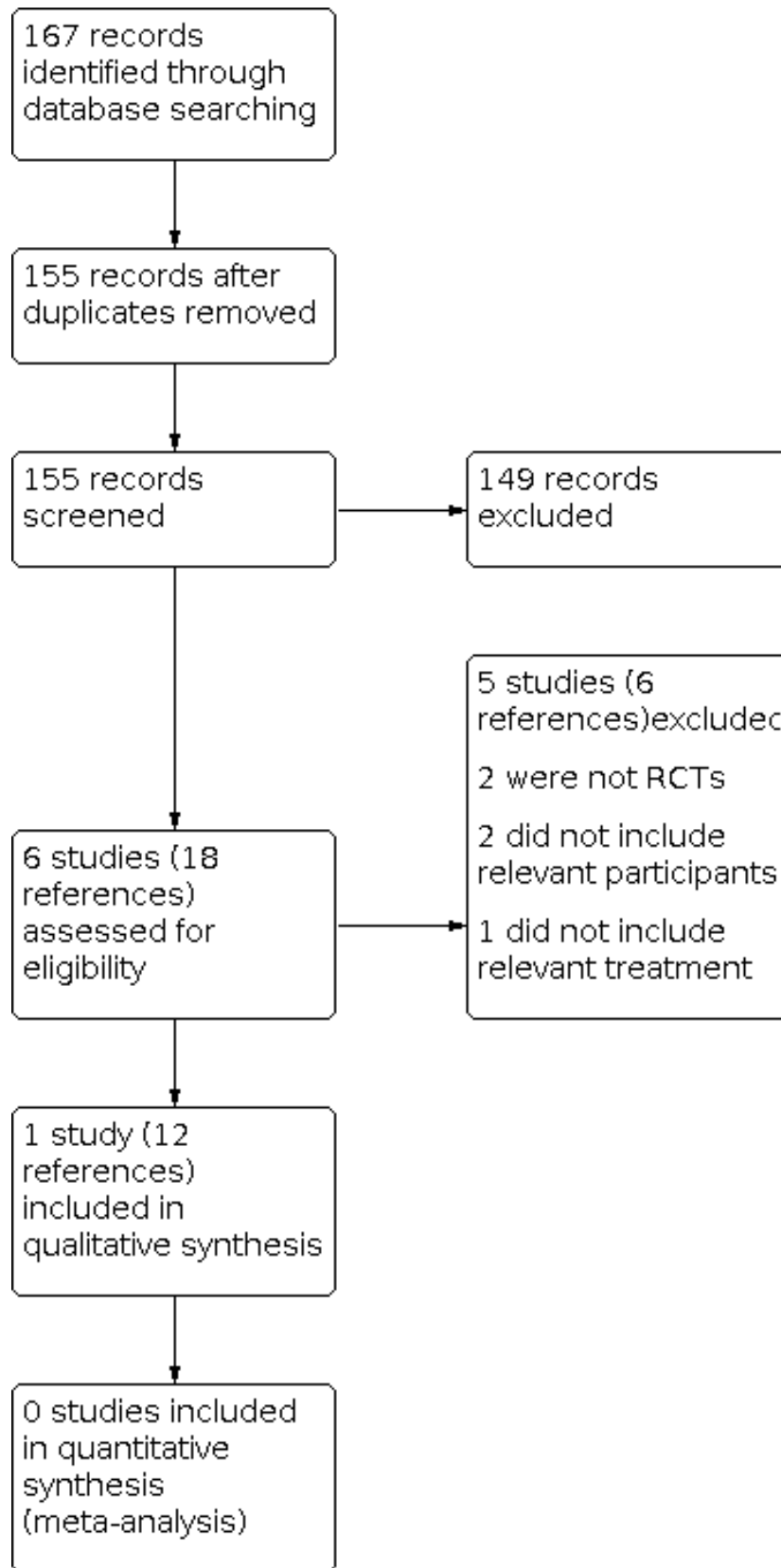
Please see the relevant tables for further information (Characteristics of included studies; Characteristics of excluded studies).

Results of the search

We identified a total of 167 references from the search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register. We identified no further studies from the searches of international trials databases. After initial consideration, we removed duplicates and were left with 155 records; of these 149 were not relevant and we discounted these (Figure 1). We examined the remaining six studies (18 references), and included

one study (12 references) and excluded five studies (six references) ([Characteristics of included studies](#); [Characteristics of excluded studies](#)).

Figure 1. Study flow diagram.



Included studies

We included a placebo-controlled RCT of long-term nebulised aztreonam lysine (AZLI), which was funded by the makers of AZLI (Tullis 2014). In this study, 100 participants were included (52 AZLI, 48 placebo) across 35 adult and paediatric centres in North America. A total of 61% of participants were male, with ages ranging from 6 years to 57 years old.

Participants were randomised to receive either 24 weeks of continuous treatment of nebulised AZLI 75 mg three times a day or placebo. The primary endpoint was mean change in FEV₁ % predicted. Key secondary outcomes were number of days to antibiotic use for respiratory exacerbations, hospitalisations, respiratory symptoms and change in sputum microbiology. A blinded medical reviewer adjudicated whether the use of antibiotics and hospitalisations were due to respiratory

exacerbations. No restrictions on additional antibiotic use were imposed.

Excluded studies

A total of five studies were excluded. Two studies were excluded as, on further examination, they were not RCTs (Kun 1984; Waters 2017); two studies did not concern the population under review (Adeboyeke 2001; Burns 1999); and one study design did not include a relevant intervention (Ledson 2002) (Characteristics of excluded studies).

Risk of bias in included studies

The overall risk of bias in the included study was assessed as 'low'. The study authors did report industry funding; however, the randomisation, blinding and outcome adjudication procedures were all conducted and reported appropriately. Further details can be found in the Characteristics of included studies and in Figure 2.

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



Allocation

Sequence generation

The included study stratified randomisation by region. The authors justified this approach as an attempt to mitigate different treatment-centre approaches for managing chronic *Burkholderia* species infection. Participants were assigned randomly 1:1 to either treatment or placebo. The sequence generation method is not reported and the risk of bias is therefore unclear.

Allocation concealment

Allocation concealment was not reported and we therefore judged the study to have an unclear risk of bias.

Blinding

Participants, investigators and outcome adjudicators were all blinded to allocation. Risk of bias was therefore considered to be low for this domain.

Incomplete outcome data

The included study reported that 14 participants (14%) did not continue treatment for the 24-week study period, given the nature of the study population this does not seem excessive. Primary outcome data are reported for all participants; however, the primary outcomes results were adjusted to account for completed days in the study. One secondary outcome was reported for less than half of all participants (change in *Burkholderia* species sputum density at week 24), which the authors reported was due to inability to provide a sputum sample of sufficient quality for sputum density analysis. Risk of bias was therefore considered to be unclear for this domain.

Selective reporting

After review of the manuscript, supplementary material and prior results presented at conferences we found no evidence of selective reporting of outcomes. There was no statistical analysis of differences in safety outcomes reported. Our own analysis confirmed no overall difference in adverse events. The risk of bias for this domain was therefore considered to be low.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

See: [Summary of findings 1 Summary of findings - AZLI compared with placebo for chronic *Burkholderia cepacia* complex infection in people with CF](#)

The certainty of the evidence has been graded for those outcomes included in the summary of findings table. For the definitions of these gradings, please refer to the summary of findings table ([Summary of findings 1](#)).

AZLI versus placebo

One study (100 participants) was included in the review ([Tullis 2014](#)).

Primary outcomes

1. Lung function

a. FEV₁

i. Absolute change in volumes, % predicted or both

The included study did not report this outcome.

ii. Relative change in volumes, % predicted or both

The study reported the relative change in % predicted FEV₁ from baseline to week 24, expressed as the mean area under curve corrected for baseline and adjusted for number of days on study. There was no statistically significant difference between the groups, MD 0.91% (95% -3.15 to 4.97) (moderate-certainty evidence) ([Analysis 1.1](#)).

2. Pulmonary exacerbations

a. Time to next exacerbation

The included study reported median days to next antibiotic use for respiratory exacerbation (as adjudicated by a blinded medical reviewer). The estimated number of median days to next antibiotic

use was for 24 days fewer in the placebo arm, however, this difference was not statistically significant (P = 0.266) (moderate-certainty evidence).

b. Hospitalisations

Total number of respiratory hospitalisations, number of days hospitalised for respiratory exacerbations, number and proportion of participants hospitalised at least once, and respiratory hospitalisation rate per participant year were all reported. At 24 weeks, no statistically significant differences were reported, RR 0.88 (95% CI 0.53 to 1.45) (moderate-certainty evidence) ([Analysis 1.2](#)).

c. Exacerbation rate

Exacerbation rate was not reported.

d. IV antibiotic use

IV antibiotic use was not reported separately. Instead a composite of number of unique days of IV, oral or inhaled antibiotics (or both) was reported. There were no statistically significant differences reported.

3. Adverse events

Adverse events were reported in detail, however, no statistical analysis of differences between groups is reported in the original paper. Our own analysis revealed no statistically significant differences in overall adverse events between groups ([Analysis 1.4](#)) (moderate-certainty evidence) ([Summary of findings 1](#)).

a. mild: transient event, no treatment change, e.g. rash, nausea, diarrhoea

The study reported a number of mild adverse events (cough, sputum increase, pyrexia, oropharyngeal pain, dyspnoea, haemoptysis, chest discomfort, nasal congestion, nausea, fatigue, wheezing, decreased appetite, rhinorrhoea, sinus congestion, sinus headache, chest pain, lung disorder, respiratory tract congestion, chills, headache and rales). At 24 weeks, wheeze was statistically significantly higher in the AZLI group compared to placebo, RR 3.61 (95% CI 1.06 to 12.34) ([Analysis 1.4](#)), however other common adverse events including cough (RR 1.15 (95% CI 0.87 to 1.52)), dyspnoea (RR 1.01 (95% CI 0.55 to 1.87)) and increased sputum (RR 1.25 (95% 0.79 to 1.96)) were all similar. It was noted in the trial report that "...The wheezing observed among AZLI-treated subjects appeared to be associated with underlying disease (asthma or prior history of wheezing), was associated with a viral infection, or was one of multiple symptoms reported for acute pulmonary exacerbation...".

b. moderate: treatment discontinued, e.g. nephrotoxicity, ototoxicity, hepatitis, visual impairment

At 24 weeks, the study reported no difference between treatment groups, there were five participants in the AZLI arm who discontinued due to adverse events, no discontinuations were seen in the placebo group, RR 11.90 (95% CI 0.68 to 209.61) ([Analysis 1.4](#)).

c. severe: causing hospitalisation or death

The study reported that severe adverse events mainly consisted of respiratory exacerbations and were similar between groups at 24 weeks, RR 1.08 (95% CI 0.49 to 2.37) ([Analysis 1.4](#)). Other severe adverse events included one life-threatening adverse event (respiratory failure) and two deaths, all of which occurred in the AZLI treatment group.

Secondary outcomes

1. Mortality

Mortality was reported in crude rates. Our own analysis revealed no statistically significant differences between groups at 24 weeks, RR 5.41 (95% CI 0.27 to 109.87) (moderate-certainty evidence) (Analysis 1.5).

2. QoL

a. Validated QoL score (e.g. CFQ-R, CRISS score)

Relative change from baseline to week 24 for the CFQ-R respiratory symptoms scale score was presented; no significant differences were reported, MD 0.18 (95% CI -4.37 to 4.73) (Analysis 1.6).

3. BCC culture

a. Sputum density of BCC

The authors presented the average change in Log₁₀*Burkholderia* species CFU/g sputum from baseline to week 24. No significant differences were reported (at 24 weeks), MD 0.93 (95% -0.57 to 2.43); however, it was noted that this analysis included only 15 participants in the AZLI group and 20 in the placebo group (Analysis 1.7).

4. Changes in inflammatory markers

a. Sputum or bronchoalveolar lavage (BAL) samples

The included study did not report this outcome.

b. Serum or blood

The included study did not report this outcome.

DISCUSSION

Summary of main results

The aim of this review was to assess the evidence for the long-term antibiotic therapy for chronic infection with BCC. Despite extensive searches of the literature we were only able to include one study suitable for inclusion in the review (Summary of findings 1). The included study compared 24 weeks of AZLI with placebo in people with CF and chronic BCC infection. The study appeared well-conducted and reported most of the outcomes of interest to this review. There were no statistically significant differences between treatment groups and placebo in terms of lung function or exacerbations. AZLI appeared to be generally well-tolerated, however, wheeze was significantly higher in the AZLI group compared to placebo.

Overall completeness and applicability of evidence

As we were only able to include one study in this review, there is a clear need for more evidence in this field. The included study investigated the use of one intervention in a broad group of

participants. The availability of an increasing array of nebulised antibiotics for people with CF warrants further trials of their use in this population.

Quality of the evidence

We were only able to include one study, which, although well-conducted, makes it likely that further studies may change the estimated effect size. Given the certainty of evidence was assessed to be moderate across all outcomes, future research is likely to have an important impact on our estimates and conclusions.

Potential biases in the review process

We are unaware of any potential biases.

Agreements and disagreements with other studies or reviews

There are no other reviews in this setting and little in the way of observational data. Our findings of a general lack of evidence for the treatment of chronic BCC infection are in keeping with reviews of other aspects of care of people with CF and BCC (Lord 2020; Regan 2019).

AUTHORS' CONCLUSIONS

Implications for practice

We found insufficient evidence from the literature to determine an effective strategy for antibiotic therapy in chronic *Burkholderia cepacia* complex infection.

Implications for research

Although the included study did not report any positive findings, it served to confirm that large randomised controlled trials can be performed in this population. The high concurrent antibiotic use in the included study may make the exacerbation outcomes difficult to define and difficult to compare with other studies. The recent expansion in available nebulised antibiotics, as well as products currently in clinical trial phase should mean further clinical trials are feasible in the future.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Tullis 2014

Study characteristics

Methods	RCT Conducted in 35 centres (USA: 34; Canada:1 (Feb 2010 - Sept 2011))
Participants	100 participants (48 given AZLI treatment; 52 given placebo) Eligible participants ≥ 6 years of age had documented CF and chronic infection with <i>Burkholderia</i> spp. 61 participants were male
Interventions	24 weeks of continuous treatment with 75 mg inhaled AZLI (3 times a day) or placebo

Tullis 2014 (Continued)

Followed by a 24-week extension period of open-label AZLI treatment for all participants (weeks 24 - 48); and a 4-week follow-up period (weeks 48 - 52)

Outcomes	<p>Primary outcome was change in lung function (FEV₁) at 24 weeks</p> <p>Secondary outcomes included: number of respiratory exacerbations requiring IV, oral or inhaled antibiotics (or both); number of respiratory hospitalisations; AUC_{ave} through week 24 for CF Questionnaire-Revised (CFQ-R) Respiratory Symptoms scores; time to respiratory exacerbation requiring IV, oral or inhaled antibiotics (or both); and adverse events</p>
Notes	The study was funded by Gilead Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not clear how sequences were generated
Allocation concealment (selection bias)	Unclear risk	Not clear how allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded with identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded medical reviewer for subjective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Some outcomes reported with significantly reduced participants. Overall, 84% of participants completed the trial and continued onto the extension period)
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other potential sources of bias were identified

AUC_{ave}: average area under the curve

AZLI: aztreonam lysine

FEV₁: forced expiratory volume in one second

RCT: randomised controlled trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Adeboyeke 2001	Not relevant participants
Burns 1999	Not relevant participants
Kun 1984	Not a RCT
Ledson 2002	Not a relevant intervention

Study	Reason for exclusion
Waters 2017	Not a RCT

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. AZLI versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Change in FEV₁	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1.1 At 24 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.2 Participants hospitalised for respiratory exacerbation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2.1 At 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3 Overall adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3.1 At 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Adverse events (by severity)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.1 Mild: cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.2 Mild: wheeze	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.3 Mild: dyspnoea	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.4 Mild: sputum increased	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.5 Moderate: discontinuation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4.6 Severe: severe adverse events or life-threatening	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5 Mortality	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5.1 At 24 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 QoL	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 At 24 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Sputum density of BCC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 At 24 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: AZLI versus placebo, Outcome 1: Change in FEV₁

Study or Subgroup	AZLI			Control			Mean Difference IV, Fixed, 95% CI [%]	Mean Difference IV, Fixed, 95% CI [%]
	Mean [%]	SD [%]	Total	Mean [%]	SD [%]	Total		
1.1.1 At 24 weeks Tullis 2014	0.16	10.28	47	-0.75	10.3	52	0.91 [-3.15, 4.97]	

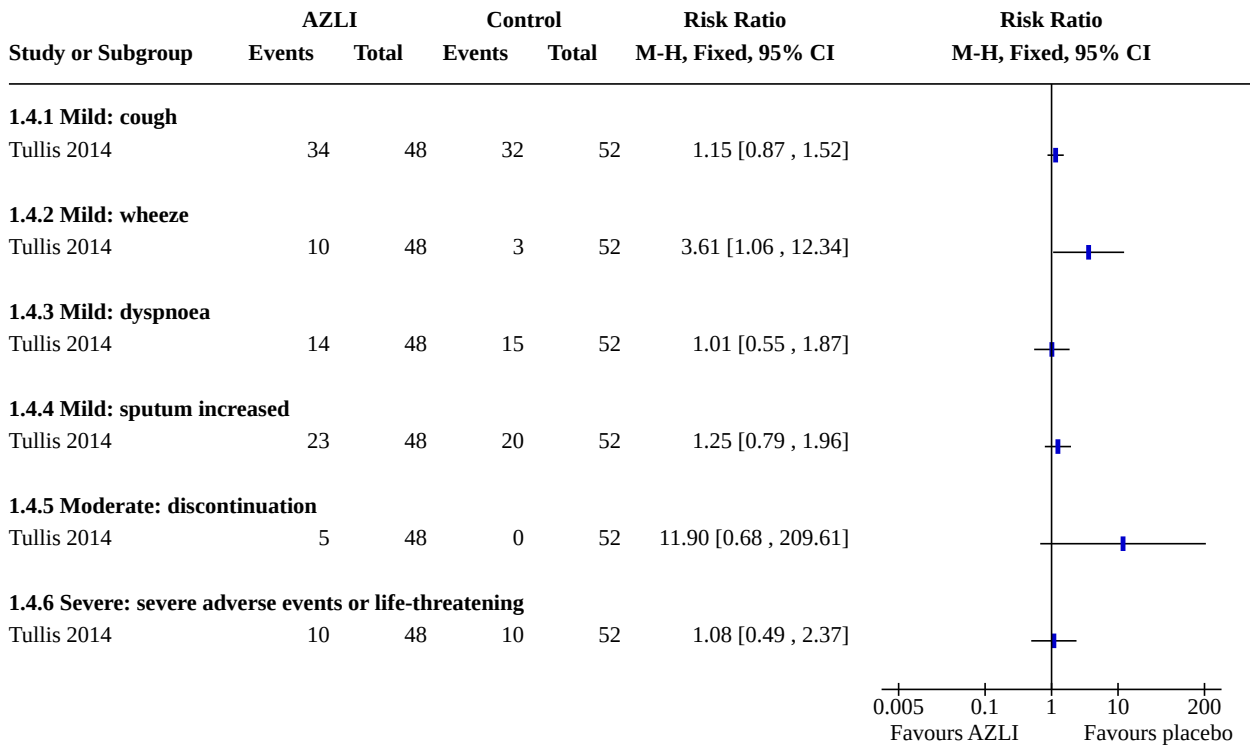
Analysis 1.2. Comparison 1: AZLI versus placebo, Outcome 2: Participants hospitalised for respiratory exacerbation

Study or Subgroup	AZLI		Control		Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
1.2.1 At 24 weeks Tullis 2014	17	48	21	52	0.88 [0.53, 1.45]	

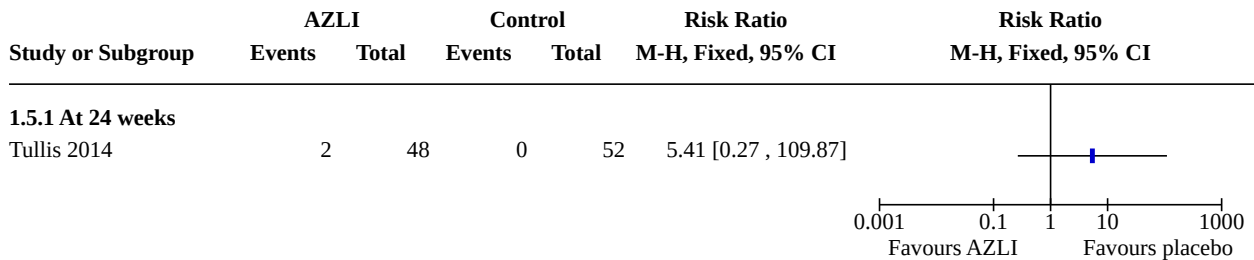
Analysis 1.3. Comparison 1: AZLI versus placebo, Outcome 3: Overall adverse events

Study or Subgroup	AZLI		Control		Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
1.3.1 At 24 weeks Tullis 2014	47	48	47	52	1.08 [0.98, 1.19]	

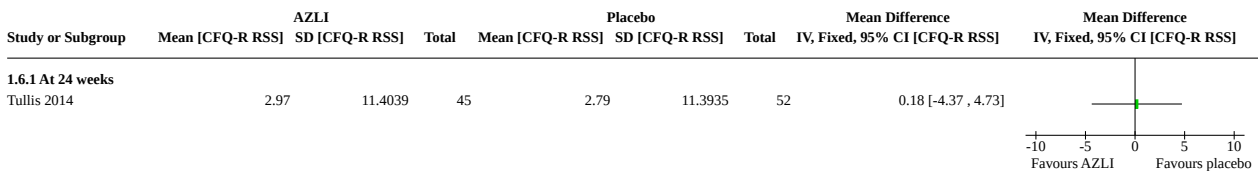
Analysis 1.4. Comparison 1: AZLI versus placebo, Outcome 4: Adverse events (by severity)



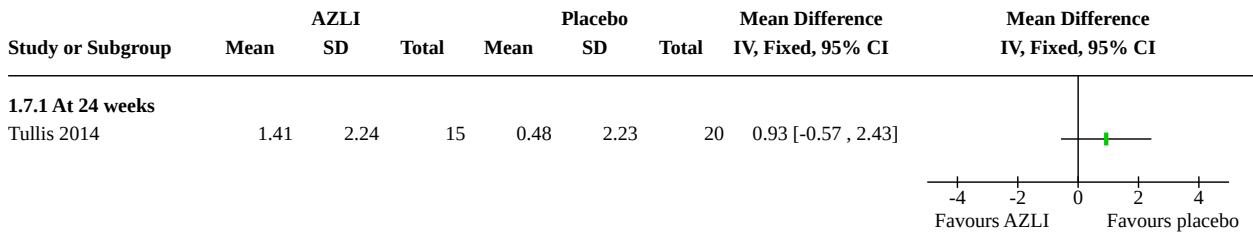
Analysis 1.5. Comparison 1: AZLI versus placebo, Outcome 5: Mortality



Analysis 1.6. Comparison 1: AZLI versus placebo, Outcome 6: QoL



Analysis 1.7. Comparison 1: AZLI versus placebo, Outcome 7: Sputum density of BCC



APPENDICES

Appendix 1. Search strategies - trial registries

Registry	Search terms	Date of most recent search
WHO ICTRP	Search terms: burkholderia OR cepacia	22 October 2021
ClinicalTrials.gov	Advanced Search form Condition or disease: cystic fibrosis Other terms: burkholderia OR cepacia Study type: Interventional Studies (Clinical Trials)	22 October 2021

WHAT'S NEW

Date	Event	Description
2 December 2021	New citation required but conclusions have not changed	For this update only minor changes were made throughout the review and our conclusions remain the same.
2 December 2021	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Register identified 23 potentially-relevant references, none of which were relevant for any section of the review. No additional results were found from searches of trials registries.

HISTORY

Protocol first published: Issue 8, 2018
Review first published: Issue 6, 2019

CONTRIBUTIONS OF AUTHORS

FF conceived the review and designed the protocol with input and advice from DN. MS provided advice regarding statistical methods. FF and DN wrote the manuscript (original protocol and review as well as subsequent updates).

DECLARATIONS OF INTEREST

All authors (FF, MS, DN) declare no potential conflict of interests.

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Internal sources

- None, Other

No Internal Sources of Funding

External sources

- National Institute for Health Research, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects]; *Burkholderia cepacia; *Cystic Fibrosis [complications] [drug therapy]; Cystic Fibrosis Transmembrane Conductance Regulator; Persistent Infection; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans; Male