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Treatment for chronic methicillin-sensitive *Staphylococcus aureus* pulmonary infection in people with cystic fibrosis (Review)

Ahmed MI, Mukherjee S

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[Intervention Review]

Treatment for chronic methicillin-sensitive *Staphylococcus aureus* pulmonary infection in people with cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is an inherited life-threatening multisystem disorder with lung disease characterized by abnormally thick airway secretions and persistent bacterial infection. Chronic, progressive lung disease is the most important cause of morbidity and mortality in the condition and is therefore the main focus of clinical care and research. *Staphylococcus aureus* is a major cause of chest infection in people with cystic fibrosis. Early onset, as well as chronic, lung infection with this organism in young children and adults results in worsening lung function, poorer nutrition and increases the airway inflammatory response, thus leading to a poor overall clinical outcome. There are currently no evidence-based guidelines for chronic suppressive therapy for *Staphylococcus aureus* infection in cystic fibrosis such as those used for *Pseudomonas aeruginosa* infection. This is an update of a previously published review.

Objectives

To assess the evidence regarding the effectiveness of long-term antibiotic treatment regimens for chronic infection with methicillin-sensitive *Staphylococcus aureus* (MSSA) infection in people with cystic fibrosis and to determine whether this leads to improved clinical and microbiological outcomes.

Search methods

Trials were identified by searching the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register, MEDLINE, Embase, handsearching article reference lists and through contact with local and international experts in the field. Date of the last search of the Group's Cystic Fibrosis Trials Register: 09 February 2018.

We also searched ongoing trials databases. Date of latest search: 20 May 2018.

Selection criteria

Randomised or quasi-randomised controlled trials comparing any combinations of topical, inhaled, oral or intravenous antimicrobials used as suppressive therapy for chronic infection with methicillin-sensitive *Staphylococcus aureus* compared with placebo or no treatment.

Data collection and analysis

The authors independently assessed all search results for eligibility. No eligible trials were identified.

Main results

The searches identified 58 trials, but none were eligible for inclusion in the current version of this review.

Authors' conclusions

No randomised controlled trials were identified which met the inclusion criteria for this review. Although methicillin-sensitive *Staphylococcus aureus* is an important and common cause of lung infection in people with cystic fibrosis, there is no agreement on how best to treat long-term infection. The review highlights the need to organise well-designed trials that can provide evidence to support the best management strategy for chronic methicillin-sensitive *Staphylococcus aureus* infection in people with cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Treatment for chronic *Staphylococcus aureus* chest infection in people with cystic fibrosis

Review question

We looked for evidence to see whether long-term antibiotic treatment for chronic infection with methicillin-sensitive *Staphylococcus aureus* (MSSA) in people with cystic fibrosis would lead to improved clinical outcomes and better results for measures of infection

Background

Cystic fibrosis is an inherited condition that causes thick mucus to build up in the lungs leading to persistent infection with bacteria. Methicillin-sensitive *Staphylococcus aureus* (also known as MSSA), is the name given to a particular bacteria which is a common cause of lung infection in people with cystic fibrosis. It can cause long-term infection in people with cystic fibrosis which leads to worsening lung function and poor overall clinical outcome. There are currently no guidelines based on trial results to inform clinicians how best to treat this infection in people with cystic fibrosis. This is an updated version of the review.

Search date

The evidence is current to: 09 February 2018.

Study characteristics

We found 58 trials in our searches, but could not find any which compared different treatments for this condition in people with cystic fibrosis. Therefore, none of these trials were eligible for inclusion in the current version of this review.

Key results

Although methicillin-sensitive *Staphylococcus aureus* is an important and common cause of lung infection in people with cystic fibrosis, there is no agreement on how best to treat long-term infection. The review highlights the need to organise well-designed trials to decide the best management strategy for chronic methicillin-sensitive *Staphylococcus aureus* infection in people with cystic fibrosis.

BACKGROUND

Please refer to the glossary for an explanation of terms (Appendix 1).

Description of the condition

Cystic fibrosis (CF) is an inherited life-threatening multisystem disorder caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on the long arm of chromosome 7 (Lommatzsch 2009). It is the most common autosomal recessive inherited condition in people of Northen European descent, with a gene carrier rate of 1 in 25 people and affecting around 1 in 2500 newborns in the UK and 1 in every 3500 in the USA (Farrell 2008; Ratjen 2003). The most important clinical feature of this genetic abnormality is lung disease, which is characterised by abnormally thick airway secretions, persistent bacterial infection and lung inflammation. Chronic, progressive lung disease is the main cause of morbidity and mortality in CF and is therefore the main focus of clinical care and research (Accurso 2007).

Staphylococcus aureus is a major cause of chest infection in people with CF. It is a ubiquitous commensal bacterium and is a frequent benign coloniser of the anterior nares, being present in approximately 37% of children aged 1 to 19 years (Kuehnert 2006). People with CF carry *S aureus* mostly in the oropharynx (Ridder-Schaphorn 2007).

S aureus is categorised into two groups, methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA). (Please note: methicillin is now the international non-proprietary name of the drug formerly known as meticillin). The reported prevalence of chronic MSSA (defined as three or more recorded isolates) in the UK is about 15% in people with CF, while MRSA (defined as any single isolate) accounted for 2.7% (CF Trust 2016). In the USA the prevalence was far greater with 70% and 26% for MSSA and MRSA, respectively (CF Foundation 2016). The CF Foundation data shows that the prevalence of *S aureus* has been increasing over the last two decades, some of this increase in prevalence may be due to improvement in the detecting and reporting of *S aureus*.

Lung infection with *S aureus* is a frequent problem in people with CF, particularly during the first decade of life (Szaff 1982) and causes chronic, recurrent endobronchial infections (Kahl 2010; Razvi 2009). Early lower airway infection with this organism in young children with CF results in worsening lung function, poorer nutrition and increases the airway inflammatory response (Gangell 2011; Wong 2013). Furthermore, there is an increase in the incidence of co-infection with *Pseudomonas aeruginosa* as the individual ages (CF Foundation 2013). The presence of both *P aeruginosa* and *S aureus* increases the concentrations of lower airway inflammatory markers and contributes to morbidity (Sagel 2009a).

Description of the intervention

Appropriate antibiotic therapy against the bacterial pathogens in the respiratory tract is vital in managing CF lung disease (Ratjen 2006). Various antibiotics have been used to treat *S aureus* including oxacillin, amoxicillin-clavulanic acid, linezolid, vancomycin, rifampicin, cephalosporins and fusidic acid. Ivacaftor, a CFTR potentiator, has also been shown to have antimicrobial properties against *S aureus* (Hubert 2018; Thakare 2017).

During chronic infection, *S aureus* is subjected to additional selective pressures resulting from antibiotic interventions, host immunity and the presence of other microbes in the airways.

Currently in the UK, children are prescribed prophylactic anti-staphylococcal antibiotics (flucloxacillin) from diagnosis until three years of age to reduce the incidence of infection with MSSA. The prophylactic therapy against *S aureus* has not been adopted by clinical practice guidelines in the USA in anticipation that this may lead to an increase in colonisation of *P aeruginosa* (Flume 2007; Stutman 2002; Ratjen 2001). However, there is currently no reliable evidence that flucloxacillin prophylaxis increases the incidence of *P aeruginosa* (Smyth 2012; Smyth 2005). At present there are no antibiotic regimens in place for chronic suppressive therapy.

How the intervention might work

Antibiotics are the mainstay of management of CF. There has been a significant increase in the life expectancy of people with CF, due partly to the aggressive use of antibiotics in the treatment of respiratory infections (Gibson 2003). The aim of treatment in chronic infection is to reduce the microbial load in the lung, thereby reducing lung damage and the rate of worsening of lung function. These outcomes should be associated with improvement in quality of life.

The use of long-term antibiotics, which includes the use of macrolides like azithromycin and inhaled tobramycin, has been proved to be helpful in managing chronic *P aeruginosa* infection (Ramsey 1999). Macrolides such as azithromycin also have a potential anti-staphylococcal activity (in people who are *P aeruginosa*- naive as well as those with chronic infection).

The effects of chronic suppressive antibiotic therapy on the CF lung microbiome and related clinical outcomes are unclear.

Why it is important to do this review

Data on prevalence of *S aureus* suggests an increase of *S aureus* prevalence in people with CF in the USA (CF Foundation 2016) and a variable prevalence of chronic *S aureus* infection in Europe ranging between 15% and 67% (Zolin 2015). However, there continues to be a lack of any description of chronic suppressive therapy for *S aureus* infection in CF such as that used for *P aeruginosa* infection. There are no available guidelines on which antibiotics to use for long-term treatment, the duration of treatment, the mode of delivery of antibiotics and the associated adverse effects; therefore, current clinical practice is greatly divergent. This review is made particularly relevant in the light of new information from recent studies suggesting correlation of growth of MSSA with accelerated decline in lung function (Cogen 2015).

A systematic review of the evidence for maintenance anti-staphylococcal therapy in CF will pool together any relevant clinical data to permit clinical decision-making, influence the design of future clinical trials and provide a scientific basis for the development of treatment guidelines.This is an update of a previously published review (Ahmed 2016).

OBJECTIVES

To assess the evidence regarding the effectiveness of long-term antibiotic treatment regimens for chronic MSSA infection in people with CF and to determine whether this leads to improved clinical and microbiological outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs, published or unpublished.

Types of participants

Children and adults with CF who are diagnosed clinically and confirmed by the presence of two disease-causing mutations, or by a combination of positive sweat test and recognised clinical features of CF and confirmed microbiologic evidence of *S aureus* (MSSA strains only) in clinically relevant CF respiratory cultures (spontaneous or induced sputum culture, cough or oropharyngeal swab, bronchoalveolar lavage specimen) at least three times over a 12-month period or more such that 50% of the cultures in a year are positive for MSSA prior to enrolment into the trial. People who are co-infected with *P aeruginosa* will also be included.

Types of interventions

Any combinations of topical, inhaled, oral or intravenous (IV) antimicrobials used with the objective of suppressive therapy for chronic infection with *S aureus* compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Sputum clearance of *S aureus* (as determined by negative culture at the end of treatment)
2. Pulmonary function tests
   a. forced expiratory volume at one second (FEV_1) per cent (%) predicted or litres
   b. forced vital capacity (FVC) % predicted or litres
   c. any other validated measures of pulmonary function
3. Adverse events
   a. emergence of resistant organisms
   b. other adverse events such as rashes, Stevens-Johnson type reactions, photosensitivity, tooth discolouration etc

Secondary outcomes

1. Frequency of respiratory exacerbations (as defined by Fuchs (Fuchs 1994))
2. Hospital admissions secondary to respiratory exacerbation
   a. frequency
   b. duration
3. School or work attendance
4. Quality of life (QoL) (as measured by e.g. CF Quality of Life Questionnaire-Revised (CFQR) (Quittner 2009), or any other validated QoL questionnaire)
5. Mortality
6. Nutritional parameters (centiles or z scoring)
   a. weight
   b. body mass index (BMI)
   c. height
7. Chest radiography scores
8. Days of IV antibiotics
9. New isolation of bacteria
   a. *P aeruginosa*
   b. MRSA
   c. other

Search methods for identification of studies

There was no restriction on language or publication status.

Electronic searches

We sought relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: (staphylococcus aureus OR mixed infections) AND (maintenance OR unknown).

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

Date of last search of Group's Cystic Fibrosis Trials Register: 09 February 2018.

Searches of ongoing trials databases was undertaken via clinicaltrials.gov (clinicaltrials.gov/), the International Standard Randomised Controlled Trials Number database (www.isrctn.org) and WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) using the search terms: Cystic fibrosis AND Staphylococcus aureus AND chronic.

Date of latest search: 20 May 2018.

Searching other resources

We will also contact primary authors and research institutions of any future identified trials for unpublished data. We shall contact pharmaceutical companies that manufacture anti-staphylococcal antibiotics for any information on any relevant trials. If we find any trials in the future, we shall check their reference lists to identify any further relevant trials.

Data collection and analysis

Selection of studies

Both authors (MA, SM) independently applied the selection criteria to determine the trials to be included in the review. There were no disagreements among the authors about the possible inclusion or exclusion of any individual trial.

Data extraction and management

We were not able to include any trials in this version of the review; however, if we include any in the future, we will carry out the following plans for data collection and analysis.

Both authors will use customised data extraction forms for independent data extraction and they will compare outcomes. In case of any disagreements on the suitability of a trial or risk of bias, the authors plan to reach a consensus through discussion.

For long-term treatment for chronic infection of *S aureus*, the authors will report outcome data at one month, up to three months, up to six months, up to 12 months and then annually thereafter. For future updates, if outcome data are recorded at other time periods, the authors will consider examining these as well.

In trials where required information is missing, the review authors will contact trial authors to seek this additional information.

Assessment of risk of bias in included studies

Both authors will independently determine the risk of bias using the Cochrane's tool for assessing risk of bias as described in chapter 8 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). This tool assists in the assessment of the risk of bias that may be introduced during the process of randomisation; method of allocation concealment; degree of blinding; completeness of outcome data; and selective reporting. The authors will resolve any disagreement over any aspect of the risk of bias for a given trial by discussions.

Measures of treatment effect

The authors plan to assess the distinct types of data that are generated by a wide range of outcome measures using different types of measures. The authors plan to collect data on all participants who took at least the first dose of the drug. For dichotomous data, the authors will summarise the results from the included trials as odds ratios (ORs) with 95% confidence intervals (CIs) according to the Mantel-Haenszel method. They will assess continuous outcomes (e.g. lung function, QoL) by calculating the mean difference (MD) with 95% CIs. Where trials report multiple measures of the same outcome, such as the percentage change in FEV_1 and percentage change in absolute FEV_1 volumes, the authors will calculate standardised mean differences (SMDs) with 95% CIs. They will consider absolute changes in FEV_1 in context of comparable data being available for each participant before and after the intervention so that the effect size could be calculated.

Unit of analysis issues

In this review, the unit of analysis will be the individual and not the number of episodes of a given event (e.g. infection or adverse reaction). The inclusion criteria used by the authors in this review do not permit the use of cross-over trials since they are not appropriate in the case of a highly variable and chronic condition such as CF. The review authors will also ensure that the number of participants randomised, and not the number of treatment attempts, is used to calculate CIs in the event of multiple attempts at treating the infection.

Dealing with missing data

The authors will compare trial protocols (where available) to the published report and contact trial authors where such data are missing. When this is not feasible, for continuous variables where standard deviations (SDs) are not published for the mean change from baseline, the authors will impute the missing SD using a correlation coefficient derived from another trial in the same or a different meta-analysis (where they have been reported) (Higgins 2011b).

Assessment of heterogeneity

With the inclusion of sufficient trials in the review, the authors will assess heterogeneity arising due to clinical and methodological diversity. The authors will attempt to identify statistical heterogeneity by calculating a Chi^2 test and using this value to compute the I^2 statistic (Higgins 2003). This measure describes the percentage of total variation across trials that is due to true heterogeneity rather than chance (Higgins 2003). The authors plan to employ a simplified categorisation of heterogeneity where I^2 values of under 25% are considered to be low, those between 26% and 50% to be moderate, between 51% and 75% to be substantial and those over 75% are considered to be of significant heterogeneity. This test will be used in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Assessment of reporting biases

In order to to assess reporting bias, the authors will compare the published outcome measures of the trials with those in the corresponding protocols (where available) and those mentioned in the 'Methods' sections within the published articles. Where important outcome measures are unaccounted for, they will contact the trial authors for information about the missing data. If the authors are able to include a sufficient number of trials (n = 10), they will use a funnel plot (trial effect against trial size) to assess the publication bias of each trial in accordance with the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011).

Data synthesis

The authors will use a fixed-effect model to analyse the data from the included trials if feasible. However, if they detect at least substantial statistical heterogeneity using the I^2 statistic (over 50%), the authors will apply a random-effects method.

Subgroup analysis and investigation of heterogeneity

Where the authors identify substantial heterogeneity among the included studies (I^2 statistic is at least 50%), it will be further investigated using subgroup analyses as follows:

- age of participants (dichotomised into child (under 18 years of age) and adult);
- duration of treatment, e.g. up to two weeks, up to one month, up to three months, up to six months, up to one year;
- antibiotic therapies used alone or when in combination with other antibiotics and the mode of delivery of antibiotics;
- whether or not *P aeruginosa* was also isolated along with *S aureus* (co-infection).

This will be achieved by categorising participants into the related subgroups and conducting meta-analyses on each of these groups.

Sensitivity analysis

The authors will test the robustness of their results using sensitivity analyses relating to fixed-effect versus random-effects analysis, irrespective of the number of studies that are included in the review.

Summary of findings table

The authors will use a summary of findings table to present the following outcomes:

- sputum clearance of *S aureus;*
- FEV_1;
- adverse events;
- frequency of respiratory exacerbations;
- mortality;
- BMI;
- isolation of new bacteria.

This table will be used for the main comparison (antibiotics compared to placebo) to present key information about the quality of evidence obtained from trials (using the GRADE approach), the sum of available data on all primary outcomes (listed above) and the magnitude of effect of the interventions examined in this review. If they identify any additional outcomes (desirable or undesirable) during the review process and they deem these to be important, they will include them in the table. The authors will follow the GRADE approach to assess the quality of the body of evidence from the trials, where they will be judged as high, moderate, low or very low. Authors will classify evidence from randomised trials with a low risk of bias as high quality (Schünemann 2011a; Schünemann 2011b).

RESULTS

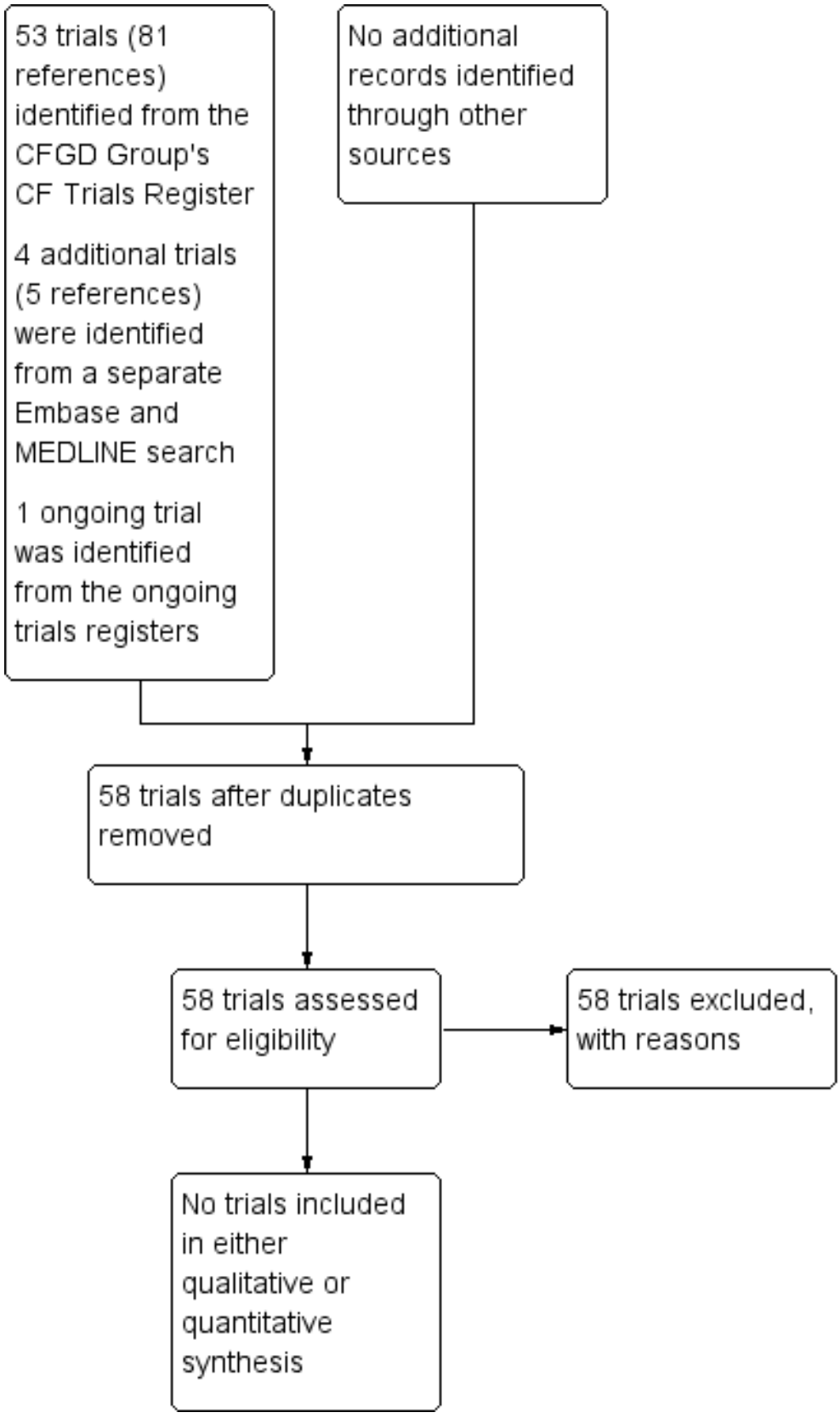
Description of studies

Results of the search

A total of 81 references to 53 trials were identified from the Cochrane Cystic Fibrosis and Genetic Disorders Group's CF Trials Register. Five references to four additional trials were identified from a separate Embase and MEDLINE search. One trial was identified from the ongoing trials registers.

Details of these trials can be found in the tables (Characteristics of excluded studies). Please also see the PRISMA diagram (Figure 1).

Figure 1. PRISMA Study flow diagram.



Included studies

The authors did not identify any eligible trials for inclusion in the current version of this review.

Excluded studies

All of the 53 trials identified in the search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's CF Trials Register were excluded; one was a trial in MRSA and not MSSA, 16 were pharmacokinetic trials, four trials were tolerability trials and the remaining 32 were excluded because the participants or interventions, or both, were not relevant to our review. None of the 53 trials that were identified by the searches of the Group's CF Trials Register had the primary goal of chronic suppressive therapy for the treatment of established MSSA infection in people with CF (*see* Characteristics of excluded studies).

Of the five additional trials identified, two had relevant participants, interventions and outcomes; but none were included as they were not randomised or controlled trials.

Risk of bias in included studies

No trials were identified which were eligible for inclusion in this review.

Effects of interventions

No trials were identified which were eligible for inclusion in this review.

DISCUSSION

Summary of main results

No RCTs were identified which met the inclusion criteria for this review. Although MSSA is an important and frequently encountered respiratory pathogen in CF, there is no consensus on suppressive therapy of chronic infection.

Quality of the evidence

For this review, there is no available evidence in the form of published RCTs and currently there are only a few observational studies.

Potential biases in the review process

No bias was encountered. We used broad search terms in this review which identified a large number of trials listed on the Cochrane Cystic Fibrosis and Genetic Disorders Group's CF Trials Register and therefore the likelihood of missing eligible trials for inclusion during searches is negligible.

Agreements and disagreements with other studies or reviews

There is a paucity of trials proposing suppressive therapy for chronic infection with MSSA.

The authors identified one small observational non-randomised and non-controlled trial, in which 13 individuals with CF and symptoms of chronic bronchopulmonary infection due to MSSA were treated with nebulized ampicillin (age range 3 to 34 years, with a mean (standard deviation) age of 14.8 (7.6) years) (Máiz 2012).This trial did not show eradication of MSSA or evidence of co-colonisation with *P aeruginosa*. There was a significant reduction in hospitalisations, sputum volume and purulence in all participants with no statistically significant differences for lung function.

One case report reported a successful long-term aerosolised ampicillin treatment of a 14-year-old girl with chronic symptomatic *S aureus* lung infection (Máiz 2009).

A cross-sectional study of microbiomes and clinical outcomes in individuals with CF colonized with MRSA compared to MSSA showed no significant difference in pulmonary function between the two groups, with significant differences in the number of hospitalisations and number of antibiotic courses over one year prior to sputum sample collection (Yenduri 2013). However, maintenance therapy of chronic infection was not reviewed during the trial.

A clinical trial examining the use of Aurexis® - a humanized monoclonal antibody that is designed to combat *S aureus* (NCT00198289) has been completed, the results have not been published. Results will include its pharmacokinetics, changes in the bacterial load of *S aureus* in sputum and changes in pulmonary function tests. However, we have already excluded the trial from our review as it is a non-randomised drug safety and pharmacokinetic trial.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no published evidence from randomised controlled trials (RCTs) to support any regimen for chronic suppressive therapy of methicillin-sensitive *Staphylococcus aureus* (MSSA) in people with cystic fibrosis (CF). There are reports of long-term antibiotic treatment and successful eradication of MSSA; however, there is no evidence of improved patient outcomes. In the absence of any adequately-powered RCTs, the treatment protocols for those with chronic infection should be based on any available non-RCT evidence, individual clinician preference and a person's characteristics.

Implications for research

This review has shown that there is a lack of evidence for maintenance therapy of chronic MSSA infection in people with CF and highlights the need for well-designed and adequately-powered RCTs.

We recommend that the following questions need to be answered.

1. What is the optimal duration of long-term antibiotic treatment of people with chronic MSSA infection in CF?
2. Does long-term suppressive therapy for chronic MSSA infection in CF improve the prognosis in these individuals?
3. Does long-term antibiotic treatment of people with chronic MSSA infection in CF have any adverse effects (i.e. emergence of resistant organisms, colonisation with other pathogens including *Pseudomonas aeruginosa*, MRSA)?

ACKNOWLEDGEMENTS

We gratefully acknowledge the support of Nikki Jahnke for her critical review and management of the review process.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Adeboyeku 2001	Not a relevant intervention - tolerability trial of differing dosages of nebulised colistin.
Amelina 2000	Not a relevant intervention or participants - difference in quality of life between home versus hospital IV treatment. No MSSA.
App 2000	Pharmacokinetic trial.
Autry 2016	Pharmacokinetic study, no MSSA
Carswell 1987	Not relevant participants - trial of *P. aeruginosa* treatment.
Chua 1990	Not a relevant intervention - used differing tonicities of inhaled antibiotics to assess airway responsiveness.
Coates 2011	Pharmacokinetic trial.
Conway 1996	Not relevant, no chronic MSSA.
Cooper 1985	Not relevant participants - trial of *P. aeruginosa* treatment.
Dalbøge 2013	Observational cohort study
Dasenbrook 2015	Treatment for chronic MRSA not MSSA.
Davis 1987	Pharmacokinetic trial.
Davis 1990	Safety and efficacy study. No microbiologic correlation.
Degg 1996	Not a relevant intervention or relevant participants - trial of long-term effects of gentamicin on hearing.
Dodd 1997	Not relevant - tolerability trial of nebulised colistin.
Dodd 1998	Not a relevant intervention or relevant participants - a compliance study.
Geller 2004	Pharmacokinetic trial.
Geller 2008	Pharmacokinetic trial.
Geller 2011a	Pharmacokinetic and tolerability study.

Study	Reason for exclusion
Geller 2011b	Not relevant participants - trial of chronic *P. aeruginosa* treatment, no MSSA and no information about chronicity of *S. aureus* infection.
Goldfarb 1986	Pharmacokinetic trial.
Gulliver 2003	Not a relevant intervention or relevant participants - testing whether nebulised IV tobramycin solution induces cough or bronchospasm, or both.
Heininger 1993	Not relevant participants.
Hjelte 1988	Not relevant participants - investigated affect of home IV antibiotics for *P. aeruginosa* on quality of life.
Huang 1979	Not relevant participants – no chronic MSSA and trial of *P. aeruginosa* treatment.
Junge 2001	Not a relevant intervention or relevant participants - effects of IV tobramycin on hearing. No MSSA.
Kapranov 1995	Not relevant participants - trial of *P. aeruginosa* treatment.
Keel 2011	Pharmacokinetic trial.
Khorasani 2009	Not relevant - No MSSA
Knight 1979	Not relevant - trial of *P. aeruginosa* treatment.
Kun 1984	Not relevant - no chronic MSSA.
Kuti 2004	Pharmacokinetic trial.
Labiris 2004	Not a relevant intervention or relevant participants, no microbiological correlation, no MSSA.
Loening -Bauke 1979	Not a relevant intervention - used cephalexin as prophylaxis.
Máiz 2009	A case report of one 14-year old boy.
Máiz 2012	Observational study.
Nathanson 1985	Not relevant participants - trial of *P. aeruginosa* treatment.
NCT00198289	Non randomised pharmacokinetic trial
Pai 2006	Pharmacokinetic trial.
Popa 2001	Not relevant – no MSSA.
Postnikov 2000	Not a relevant intervention or relevant participants – an efficacy and tolerability study of Pefloxacin. No chronic MSSA.
Postnikov 2001a	Not a relevant intervention or relevant participants - trial on chondrotoxicity of fluoroquinolones. No MSSA.
Postnikov 2001b	Not a relevant intervention or relevant participants - study of arthrotoxicity of fluoroquinolones.
Prayle 2016	MSSA not present, pharmacokinetic trial.

Study	Reason for exclusion
Ramstrom 2000	Not a relevant intervention or relevant participants - a compliance study.
Roberts 1993	Pharmacokinetic trial.
Romano 1992	Not relevant participants - trial of *P. aeruginosa* treatment.
Rosenfeld 2006	Pharmacokinetic study
Sagel 2009	Not a relevant intervention, tolerability trial.
Salh 1992	Not relevant participants - MSSA not required for entry into trial.
Sharma 2016	Not relevant - no MSSA
Singh 2013	No chronic MSSA. No relevant outcomes.
Smith 1997	Pharmacokinetic trial.
Stutman 1987	Pharmacokinetic trial. Not relevant participants, chronic MSSA not a requirement for entry.
Vitti 1975	Pharmacokinetic trial.
Willekens 2013	Not relevant participants, no relevant outcomes
Wood 1996	Not a relevant intervention or participants, trial of toxic effects of long-term gentamicin therapy.
Yenduri 2013	Participants in the trial and outcomes were not relevant to review.

IV: intravenous
MRSA: methicillin-resistant *Staphylococcus aureus*
MSSA: methicillin-sensitive *Staphylococcus aureus*
P. aeruginosa: *Pseudomonas aeruginosa*
S. aureus: Staphylococcus aureus

APPENDICES

Appendix 1. Glossary

Term	Explanation
autosomal recessive	autosomal recessive is one of several ways that a trait, disorder, or disease can be passed down through family genes; in an autosomal recessive disorder two copies of an abnormal gene must be present in order for the disease or trait to develop
bacterial pathogen	a bacteria that can produce disease
bronchoalveolar lavage	a procedure in which a bronchoscope (a tube) is passed through the mouth or nose into the lungs and fluid is squirted into a small part of the lung and then collected for examination
chi-squared test	a statistical test to ascertain whether the association between two variables is true

(Continued)

correlation coefficient	a statistical measure of the degree of association between two continuous variables
endobronchial	located within a bronchus (one of two large air tubes that begins at the end of the windpipe and branch into the lungs)
GRADE	GRADE is a systematic and explicit approach to making judgements about quality of evidence and strength of recommendations
microbiome	the micro-organisms found in a particular body or part of the body
morbidity	illness, diseased state
oropharynx	the part of the throat that is at the back of the mouth
oropharyngeal swab	a swab taken from the throat at the back of the mouth
photosensitivity	how the skin reacts to light
prophylactic	preventative
pulmonary exacerbations	flare ups of lung disease
respiratory cultures	a test to detect and identify bacteria or fungi that infect the lungs or breathing passages

WHAT'S NEW

Date	Event	Description
23 July 2018	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified five new references which were potentially eligible for inclusion in the review. Three references were additional references to already excluded studies (Dasenbrook 2015; Geller 2011b; Prayle 2016) and two new studies each with a single reference have been excluded (Khorasani 2009; Sharma 2016). Additional searches identified a single study which was excluded (Autry 2016).
23 July 2018	New citation required but conclusions have not changed	We have not included any new data in this update, hence our conclusions remain the same.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	**WHO WILL UNDERTAKE THE TASK?**
Protocol stage: draft the protocol	Molla Imaduddin Ahmed Saptarshi Mukherjee

Review stage: select which trials to include	Molla Imaduddin Ahmed Saptarshi Mukherjee
Review stage: extract data from trials	Molla Imaduddin Ahmed Saptarshi Mukherjee
Review stage: enter data into RevMan	Molla Imaduddin Ahmed Saptarshi Mukherjee
Review stage: carry out the analysis	Molla Imaduddin Ahmed Saptarshi Mukherjee
Review stage: interpret the analysis	Molla Imaduddin Ahmed Saptarshi Mukherjee
Review stage: draft the final review	Molla Imaduddin Ahmed Saptarshi Mukherjee
Update stage: update the review	Molla Imaduddin Ahmed Saptarshi Mukherjee

DECLARATIONS OF INTEREST

Molla Imaduddin Ahmed declares no known potential conflict of interest.

Saptarshi Mukherjee declares no known potential conflict of interest.

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INDEX TERMS

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*Staphylococcus aureus [drug effects]; Anti-Bacterial Agents [*therapeutic use]; Cystic Fibrosis [*microbiology]; Methicillin [*therapeutic use]; Respiratory Tract Infections [*drug therapy] [microbiology]; Staphylococcal Infections [*drug therapy]

MeSH check words

Humans