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Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis (Review)

Lo DKH, Hurley MN, Muhlebach MS, Smyth AR

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[Intervention Review]

Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis is an inherited recessive disorder of chloride transport that is characterised by recurrent and persistent pulmonary infections from resistant organisms that result in lung function deterioration and early mortality in sufferers.

Meticillin-resistant *Staphylococcus aureus* (MRSA) has emerged as, not only an important infection in long-term hospitalised patients, but also as a potentially harmful pathogen in cystic fibrosis, and has been increasing steadily in prevalence internationally. Chronic pulmonary infection with MRSA is thought to confer cystic fibrosis patients with a worse overall clinical outcome and, in particular, result in an increased rate of decline in lung function. Clear guidance for the eradication of MRSA in cystic fibrosis, supported by robust evidence from good quality trials, is urgently needed.

Objectives

To evaluate the effectiveness of treatment regimens designed to eradicate MRSA and to determine whether the eradication of MRSA confers better clinical and microbiological outcomes for people with cystic fibrosis.

Search methods

Randomised and quasi-randomised controlled trials were identified by searching the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register, PUBMED, 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: 04 September 2014.

Selection criteria

Randomised or quasi-randomised controlled trials comparing any combinations of topical, inhaled, oral or intravenous antimicrobials with the primary aim of eradicating MRSA compared with placebo, standard treatment or no treatment.

Data collection and analysis

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

Main results

No current published eligible trials were identified, although three ongoing clinical trials are likely to be eligible for inclusion in future updates of this review.

Authors' conclusions

We did not identify any randomised trials which would allow us to make any evidence-based recommendations. Although the results of several non-randomised studies would suggest that, once isolated, the eradication of MRSA is possible; whether this has a significant impact on clinical outcome is still unclear. Further research is required to guide clinical decision making in the management of MRSA infection in cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Interventions to clear meticillin-resistant *Staphylococcus aureus* (MRSA) from the lungs of people with cystic fibrosis

Review question

We looked for evidence to determine the effect of different ways of clearing meticillin-resistant *Staphylococcus aureus* (MRSA) from the lungs of people with cystic fibrosis.

Background

Meticillin-resistant *Staphylococcus aureus* (MRSA), is the name given to a particular bacteria which is resistant to some types of antibiotics. This is particularly worrying for people with cystic fibrosis, which is an inherited condition that causes thick mucus to build up in the lungs. It is very difficult for people with cystic fibrosis to cough up this thick mucus, making it an ideal breeding ground for bacteria, including MRSA, and making these people more prone to chest infections. It is thought that MRSA can cause more damage than other bacteria which are not resistant to antibiotics. We wanted to identify research evidence to support the best way for treating MRSA infections and also to see if this would improve the lives of people with cystic fibrosis.

Search date

The evidence is current to: 04 September 2014.

Key results

Unfortunately, we could not find any trials which compared treating MRSA to not treating MRSA, or which compared one form of treatment to another. We are unable, therefore, to make any recommendations for its management at this point in time.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common autosomal inherited condition in the Caucasian population, with a gene carrier rate of 1 in 25 and affecting around 1 in 2500 newborns in the UK (CF Trust UK 2011). It is a multisystem disorder resulting from a disruption in chloride transport at the cellular level leading to abnormal, dehydrated secretions within the lungs. This results in impaired mucociliary clearance leading to recurrent pulmonary infections, bronchiectasis and progressively deteriorating lung function, which is the main cause of the morbidity and mortality seen in CF.

Organism

The abbreviation MRSA stands for meticillin-resistant *Staphylococcus aureus* (*S. aureus*). Meticillin is an antibiotic that is no longer in clinical use, but MRSA is resistant to antibiotics within the same class. This includes flucloxacillin, which is prescribed both for prophylaxis and treatment of infection with *S. aureus* in people with CF in the UK. Furthermore, MRSA is also resistant to other antibiotics in the beta lactam family such as cephalosporins (e.g. ceftazidime) and carbapenems (e.g. meropenem). Resistance is not due to production of beta lactamase enzymes, but rather to the production of altered penicillin-binding proteins coded on the mecA gene.

Most MRSA infections in both the non-CF and CF populations have been so-called 'healthcare associated' (HA-MRSA), which occur in patients who have been hospitalised, had surgery, are on dialysis, or who have had invasive procedures. However, in recent years outbreaks of 'community-acquired' MRSA (CA-MRSA) have occurred in otherwise healthy people with no link to a healthcare facility (Chambers 2009). This distinction by patient location at time of infection is becoming increasingly difficult, given outbreaks of strains of CA-MRSA in hospitals, and the spread of HA-MRSA strains in the community through people with chronic illnesses.

It is possible to further classify MRSA according to the staphylococcal chromosome cassette *mec* (SCC*mec)* type, on which the *mec*A gene is located. Several distinct types have been described to date, of which HA-MRSA is associated with types I to III. These SCC*mec* types also encode for resistance to other classes of antibiotics, thus making HA-MRSA overall more resistant. So-called CA-MRSA carries SCC*mec* types IV and V. Although CA-MRSA usually has the smaller type IV SCC*mec* type, which lacks some of the antibiotic resistance determinants possessed by types I to III, it is also more frequently associated with the production of the virulence factor Panton-Valentine leucocidin (PVL), a cytotoxin which causes leucocyte destruction and tissue necrosis.

Although patients with MRSA have been found to require a higher intensity of treatment when compared with their meticillin-sensitive *S. aureus* (MSSA) counterparts, this is further complicated by differences observed between different MRSA types (Muhlebach 2011). For instance, the emergence of PVL-positive CA-MRSA within the CF population has been described and one report suggests this to be associated with a more severe clinical course acutely compared with PVL-negative CA- or HA-MRSA strains (Elizur 2007).

Prevalence

The prevalence of MRSA varies throughout Europe. As reported by the European Centre for Disease Prevention and Control, in the UK 25% to 50% of isolates of *S. aureus* are found to be MRSA compared to less than 1% in Norway (ECDC 2009). In the USA, the proportion of healthcare-associated *S. aureus* infections found in intensive care units that are attributable to MRSA has increased from 2% in 1974 to 64% in 2004 (Klevens 2006).

Amongst people with CF, the prevalence of chronic MSSA (defined as three or more recorded isolates) in the UK has increased from 7.3% in 2001 to 15.2% in 2009, with the prevalence of MRSA (defined as any single isolate) at 2.5% (CF Trust 2009).

The USA CF registry data from 2009 recorded any isolate of MSSA at 51.3% and any isolate of MRSA at 23.7%, with 65.8% of their CF population having positive cultures for either MSSA or MRSA (CF Foundation 2009). The most recent 2010 data reports the prevalence of MSSA at 67% and MRSA at 25.7% (CF Foundation 2010).

In Australia, the 2009 CF registry reports a MSSA prevalence of 43% and MRSA prevalence of 4.2% as a proportion of tested patients via any culture method and including any single positive isolate (Cystic Fibrosis Australia 2011).

Condition

As described above, one of the early key pathogens in CF-lung disease is MSSA, but increasingly MRSA has been cultured from the lower respiratory tracts of people with CF. The role of MRSA in CF-lung disease remains debated.

A large observational study looking at 1834 patients who had positive respiratory cultures for *S. aureus* (MRSA or MSSA) found that presence of MRSA in respiratory cultures was associated with poorer lung function, more courses of antibiotics and longer hospital stays when compared with those colonised with MSSA (Ren 2007). However, the authors were unable to conclude whether their findings were due to cause or effect.

Two studies were published in 2008 addressing this point, but came to differing conclusions (Dasenbrook 2008; Sawicki 2008). Dasenbrook suggested that chronic, though not intermittent, detection of MRSA in respiratory tract cultures of people with CF (as defined by reports from the CF Foundation Registry) is associated with poorer survival and reduced lung function (Dasenbrook 2008; Dasenbrook 2010). By contrast, Sawicki concluded that although MRSA was a marker for more aggressive therapy and may reflect increased disease severity, MRSA detection was not associated with a significant decline in lung function (Sawicki 2008).

Although both were longitudinal studies, Sawicki analysed data from an observational study of people with CF in North America (Epidemiologic Study of Cystic Fibrosis (ESCF) (Morgan 1999)) using multivariate linear regression analysis to study the impact of MRSA on lung function (forced expiratory volume in one second (FEV_1) per cent (%) predicted); whilst Dasenbrook used data from the CF Foundation Registry. One of the fundamental differences between the two studies is the inclusion criteria. Sawicki included patients for analysis who had only one positive culture for MRSA (23% of cohort) whilst Dasenbrook studied patients with three or more positive cultures, those with one or two MRSA cultures were excluded.

Despite these differences, both studies reported an increased rate of decline in FEV_1 % predicted of around 0.5% in their 'before' and 'after' MRSA groups. It is possible that this did not reach statistical significance in the Sawicki paper secondary to the smaller cohort size (593 versus 1732). An increased rate of decline of 0.8% has more recently been reported by a group in Belgium who conducted a retrospective case-control study based at a single centre (Vanderhelst 2012).

In terms of survival, Dasenbrook found that detection of MRSA from the respiratory tract of CF patients was associated with a risk of death 1.27 (95% confidence interval (CI) 1.11 to 1.45) times that of individuals in whom MRSA had never been detected (Dasenbrook 2010). Perhaps of more clinical importance however, is that they also found that patients who clear MRSA within one year have the same risk of death as those who never have a positive culture for MRSA. This emphasizes the importance and need for clear guidance on how we manage MRSA infection in CF.

Description of the intervention

Currently in the UK, children are prescribed prophylactic anti-staphylococcal antibiotics (flucloxacillin) from diagnosis until three years of age with resultant fewer isolates of *S. aureus*, though the clinical significance of this finding remains uncertain (Smyth 2003). However, the US Cystic Fibrosis Foundation recommend against the use of prophylaxis in anticipation that this may lead to an increase in colonisation of *Pseudomonas aeruginosa* (*P. aeruginosa*) (Flume 2007).

Some authors suggest a pragmatic approach would be to treat every isolate of MRSA or MSSA with eradication therapy (Solis 2003). However, this approach, with its frequent use of antibiotics, would run the risk of increasing the incidence of multi-resistant organisms that are less susceptible to treatment, whilst potentially adding to the already substantial treatment burden that people with CF face.

Certainly in the case of HA-MRSA infections, there has been encouraging progress since the introduction of stringent MRSA screening and eradication measures in hospitals. The 2010 report by the Centers for Disease Control and Prevention showed a 28% decline in invasive MRSA infections originating in hospitals between 2005 and 2008 in the USA (Kallen 2010). Whilst in the UK, the Department of Health target to reduce MRSA bloodstream infections by 50% from its peak levels in 2003 to 2004 was achieved by 2008 (Liebowitz 2009; Pearson 2009).

Why it is important to do this review

Despite the increasing prevalence of MRSA, its clinical significance remains unclear and there remains no international consensus for its management. With the increasing prevalence of resistant strains of *S. aureus*, it becomes more important for any therapeutic approaches with antibiotics to be justified with the most up-to-date evidence, especially in patients with chronic medical conditions.

A previous Cochrane review could not find enough evidence to support the use of any single or combination of therapies for eradicating nasal or extra-nasal colonisation of MRSA over another (Loeb 2003). Most studies addressing MRSA colonisation have been done in either healthy carriers or people in chronic care facilities, but not in those with chronic lung disease as seen in CF. Such reports include a variety of interventions, often focusing on nasal and skin colonisation, thus such findings may not be directly applicable to CF. However, a retrospective review of MRSA eradication practice in a single large UK adult CF centre showed some promise (Doe 2010). They used varying eradication regimes based on sensitivity patterns and individual tolerability, including stringent patient segregation and topical decolonisation, to attempt MRSA eradication from sputum and skin in CF patients. Over a 10-year period they reported an eradication rate of 81% (defined as three consecutive negative sputum and peripheral cultures over six months), though the clinical impact of what successful MRSA eradication meant for patients was not reported.

The 2008 UK CF Trust consensus statement document stated that in the absence of prospective randomised clinical trials looking at the effect on lung function which chronic carriage with MRSA confers, MRSA infection will lead to a reduction in antibiotic treatment options and a likelihood of a deterioration in lung function. It is therefore their recommendation that the eradication of MRSA should be attempted for positive cases (CF Trust 2008).

The rationale for this review is to determine the success of MRSA eradication for people with CF, and to question whether eradication confers improved clinical outcomes. This version of the review is an update of the original review (Lo 2013).

OBJECTIVES

To evaluate the effectiveness of treatment regimens designed to eradicate MRSA and to determine whether the eradication of MRSA confers better clinical and microbiological outcomes for patients with CF.

To ascertain whether attempts at eradicating MRSA can lead to increased acquisition of other resistant organisms (including *P. aeruginosa*) or increased adverse effects from drugs, or both.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials.

Types of participants

Children and adults diagnosed with CF clinically and by sweat or genetic testing with a confirmed positive microbiological isolate of MRSA on clinically relevant CF respiratory cultures (bronchoalveolar lavage (BAL), cough or oropharyngeal swab, spontaneous or induced sputum culture) specimen prior to enrolment into the trial.

We included all disease severities. We did not include patients with nasal carriage of MRSA alone in this review.

Types of interventions

Any combinations of topical, inhaled, oral or intravenous antimicrobials with the primary aim of eradicating MRSA once detected on clinically relevant CF respiratory cultures compared with placebo, standard treatment or no treatment.

Types of outcome measures

Primary outcomes

1. Eradication of MRSA (as defined by negative respiratory culture after completion of the eradication protocol)
2. Time until next positive MRSA isolate from clinically relevant respiratory culture

Secondary outcomes

1. Lung function
    i) forced expiratory volume at one second (FEV_1) % predicted
    ii) forced vital capacity (FVC) % predicted
    iii) other validated measures of lung function
2. Overall antibiotic use
3. Mortality
4. Quality of life measured using a validated tool
    i) CF Questionnaire-Revised version (CFQ-R) (Quittner 2009)
    ii) CF Quality of Life Questionnaire (CFQoL) (Gee 2000)
5. Isolation of MRSA or other organisms with new antibiotic resistant phenotypes
    i) *P. aeruginosa*
    ii) other previously uncultured organism
    iii) small colony variants
6. Growth and nutritional status
    i) weight (kg)
    ii) height (cm)
    iii) body mass index (BMI) (kg/m^2)
    iv) lean body mass (%)
    v) fat body mass (%)
7. Adverse effects to treatment
    i) mild (not requiring treatment)
    ii) moderate (requiring treatment or admission or cessation of treatment, or a combination of any of these)
    iii) severe (life-threatening)
8. Elimination of carrier status (nasal or skin)
9. Frequency of exacerbations
10. Cost of care

Search methods for identification of studies

Electronic searches

We identified relevant studies from the Group's Cystic Fibrosis Trials Register using the terms: (*Staphylococcus aureus* OR mixed infections) AND (eradication OR unknown).

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cochrane Cystic Fibrosis and Genetic Disorders Group Module. Date of the latest search of the Group's CF Register: 04 September 2014.

We
searched for relevant trials via the websites www.clinicaltrials.gov and www.isrctn.org using the search terms (Cystic Fibrosis AND MRSA). Date of latest search: 10 December 2014.

We also independently searched PUBMED, MEDLINE (1950 to December 2014) and Embase (1980 to December 2014) via the OpenAthens access management system using the search strategy detailed below - see Appendix 1. Date of latest search: 10 December 2014.

Searching other resources

We will also contact primary authors and research institutions of any future identified trials for unpublished data.

Data collection and analysis

We were unable to identify any eligible and completed trials for inclusion in this review. We have detailed our methodology for

selection of trials and also the planned methodology for data analysis should eligible studies become available in future searches.

Selection of studies

Two authors (DL, MH) independently screened trials for inclusion in this review using methods in accordance with methods described by Higgins in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Both authors independently examined the title and abstracts to exclude duplicate publications, case reports, review articles and unrelated articles. Of the remaining studies, DL and MH independently examined the full text publications to determine if they met our eligibility criteria. The authors planned to resolve any disagreements on the eligibility of studies by consulting with the third and fourth authors (MM, AS) for advice and reaching a consensus through discussion between all authors.

Data extraction and management

Should any eligible studies become available in future searches, two authors (DL, MH) will extract data using standardised data acquisition forms upon which all authors have agreed. They will resolve disagreements through discussion between all four authors. Where information is incomplete or unclear, the authors will attempt to contact the lead author of the paper where possible.

The authors plan to group outcome data into those measured at up to 14 days, up to 1 month, up to 3 months, up to 6 months and up to 12 months after MRSA therapy. All authors will consider data for inclusion which was recorded at other time intervals and highlight this in the report.

Assessment of risk of bias in included studies

The authors will assess the risk of bias using methods described in the*Cochrane Handbook for Systematic Reviews for Interventions* (Higgins 2011b). In particular each author will examine the methods to determine the adequacy of randomisation and blinding, and also whether any participants lost to follow-up are accounted for and justified. They will also seek to identify any selective reporting by comparing the full report to the protocol.

In addition, each author will independently use the 'risk of bias' assessment tool available in section 8.5 of the *Cochrane Handbook for Systematic Reviews for Interventions* in order to judge each of the described seven domains as having low, high or unclear risk of bias (Higgins 2011b).

Measures of treatment effect

For dichotomous data (e.g. eradication achieved or not), the authors plan to analyse the data on an intention-to-treat basis, irrespective of compliance or dropout secondary to adverse effects. They will sort the data based on each possible outcome event for each treatment arm and calculate the odds ratio (OR) and its 95% CI.

For continuous data, the authors plan to calculate the mean difference (MD) of effect of each variable along with its 95% CI. Where two or more studies measure the same outcome but using different scales, they aim to calculate the standardised mean difference (SMD) with its 95% CI.

The authors plan to extract ordinal and count data in all forms in which they are reported and plan to analyse these as per continuous data for common outcomes; for rare outcomes they will follow the advice in section 9.2.5 of the*Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

For time-to-event data (e.g. time to next exacerbation), they plan to calculate the hazard ratio (HR) at individual time points (at 14 days, then 1, 3, 6 and 12 months) along with its 95% CI.

Unit of analysis issues

Cross-over studies are not eligible for inclusion within this review since the authors are reviewing how efficacious the initial attempt at eradication of MRSA is when compared with placebo, usual treatment or no treatment. Subsequently, they aim to evaluate time until next positive MRSA culture and number of further courses of antibiotics required following each arm of therapy.

The authors do not plan to include cluster-randomised controlled trials. When randomisation is performed according to patient groups, certain strains of MRSA (which may differ between communities) could potentially be over-represented in either the treatment or placebo arm and hence bias the results.

Dealing with missing data

In cases where data are missing which relate to either the review's primary or secondary outcomes, the authors will attempt to contact the primary investigator for clarification. If they are not able to contact the primary investigator, they will attempt to contact the co-investigators and sponsors.

Assessment of heterogeneity

In order to assess heterogeneity between studies the authors will use the I^2 statistic and the chi-squared test. As stated in the*Cochrane Handbook for Systematic Reviews of Interventions*, the importance of the observed value of I^2 depends on (i) the magnitude and direction of effects and (ii) the strength of evidence for heterogeneity (e.g. P value for chi-squared) (Higgins 2011a). The authors will consider values of 0% to 40% to represent little to no heterogeneity, 30% to 60% moderate, 60% to 90% substantial and values of more than 90% as demonstrating considerable heterogeneity.

Assessment of reporting biases

The authors plan to assess for selective reporting of results by comparing (where available) the outcomes listed in the original protocol to those reported in the final paper. They will also search clinical trials registers for any completed studies relevant to our review that may not have been published. They plan to attempt to contact the primary investigators of identified trials to determine whether they are aware of any relevant unpublished data. This may help to identify some small studies which may not have reported statistically significant outcomes. The authors aim to identify publication bias with the construction of funnel plots, although they are wary of other potential causes for asymmetry.

Data synthesis

The authors aim to analyse extracted data using a fixed-effect meta-analysis unless the heterogeneity between studies is found to be substantial (more than 60%), at which point they will perform a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

If the authors identify a sufficient number of studies (more than 10) and also find substantial heterogeneity between studies, they will investigate this with subgroup analysis of the following:

1. eradication therapy commenced at initial acquisition versus following chronic colonisation (three or more positive cultures over a 12-month period);
2. duration of eradication therapy (up to and including 6 weeks, 7 to 12 weeks, over 12 weeks);
3. intravenous versus aerosolised versus oral administration of antibiotics;
4. efficacy of regimens which include methods for skin or nasal eradication, or both, versus those that do not.

Sensitivity analysis

Where outcome measures have been chosen based upon arbitrary values, the authors plan to re-evaluate the effect that alternative endpoints have on their findings. For instance, some studies may use a cut-off of longer than 14 days to represent successful eradication of MRSA, where the available data allows, the authors will repeat the analysis of treatment effect using different cut-offs (1, 3, 6 or 12 months).

With regards to smaller studies (20 participants in each group or less) that the authors may include in the initial meta-analyses, they aim to repeat the analyses without these smaller studies to determine their effect.

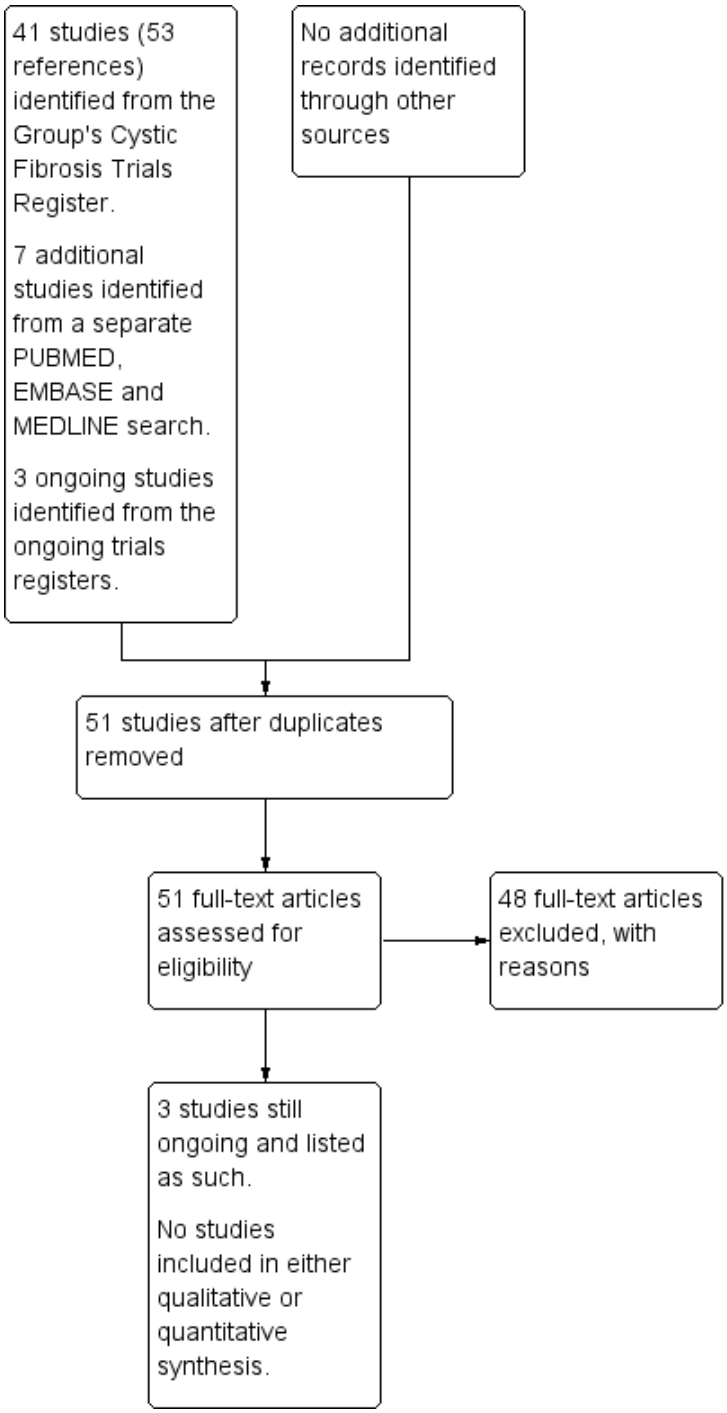
RESULTS

Description of studies

Results of the search

A total of 54 references to 41 studies were identified from the CFGD Group's CF Trials Register. Seven additional studies were identified from a separate PUBMED, EMBASE and MEDLINE search. Three ongoing studies were identified from the ongoing trials registers www.clinicaltrials.gov and www.isrctn.org. These ongoing trials may be eligible for inclusion into future versions of this review: 'Early meticillin-resistant *Staphylococcus aureus* (MRSA) therapy in cystic fibrosis (CF)' (NCT01349192), 'Persistent meticillin-resistant *Staphylococcus aureus* eradication protocol' (NCT01594827) and 'Efficacy and safety study of AeroVanc for the treatment of persistent MRSA lung infection in cystic fibrosis patients' (NCT01746095). Details of these studies can be found in the tables (Characteristics of ongoing studies). Please also see the PRISMA diagram (Figure 1).

Figure 1. Study flow diagram.



Included studies

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

Excluded studies

Of the 41 excluded studies from the results of the search of the Cystic Fibrosis and Genetic Disorders Group's CF Trials Register, 12 were pharmacokinetic studies, one was a tolerability study and the remaining 28 were excluded because the participants or interventions were not relevant to our review (See: Characteristics of excluded studies). None of the 41 studies had the primary intent of MRSA eradication in people with CF.

Of the seven additional studies identified, all had relevant participants, interventions and outcomes but these were not included as they were not randomised or controlled studies. All had the primary aim of MRSA or *S.aureus* (one study) eradication in people with CF. Two were case reports, one of a 10-year old boy (Maiz 1998) and one of a 28-year old man (Serisier 2004). Four were observational studies (Garske 2004; Macfarlane 2007; Dalbøge 2013; Vanderhelst 2013) and one was a retrospective study (Solis 2003).

Risk of bias in included studies

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

Effects of interventions

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

DISCUSSION

Summary of main results

Although MRSA is an important emerging pathogen in CF respiratory illness, there is no widely accepted consensus for its optimal management. The broad search terms used in this review identified a large number of studies listed on the Cochrane CFGD Group's CF Trials Register, unfortunately none of them were relevant or eligible for inclusion. Most of the studies identified dealt primarily with *P. aeruginosa* treatment in CF and not with MRSA.

Overall completeness and applicability of evidence

There are currently three ongoing prospective studies awaiting completion, which will potentially be eligible for inclusion in future versions of this review. One study examines the eradication of early MRSA acquisition, whilst the other two examines management of persistent infection (*see* Characteristics of ongoing studies). One of these is currently recruiting participants and is estimated to complete in March 2015 (NCT01594827) whilst the other two studies have completed patient enrolment and results are awaited (NCT01349192 and NCT01746095). All three studies will compare an active treatment group to an observational/placebo group.

Quality of the evidence

The available evidence for this review is poor, with no published randomised controlled trials and only a few observational or retrospective studies at present.

Potential biases in the review process

One of the co-authors of this review (MM) is the lead investigator of one of the ongoing clinical trials (NCT01349192).

Agreements and disagreements with other studies or reviews

Various strategies have been proposed for the eradication of MRSA when isolated from CF respiratory samples. It has become apparent from this review that these are based on anecdotal evidence or, at best, a small number of observational studies involving small numbers of participants.

The authors identified seven non-randomised and non-controlled studies; three in paediatric participants (age range 1 to 16 years), two in adults (age range 22 to 36 years) and two in mixed paediatric and adult groups. With the exception of Maiz 1998 (a case report on one 10-year old boy), and Dalbøge 2013 (a cohort study which reports on efficacy of *S.aureus* eradication, where only 0.3% of subjects were MRSA positive), the remaining five studies reported successful eradication of MRSA in, at least a proportion of, their participants (Garske 2004; Macfarlane 2007; Serisier 2004; Solis 2003; Vanderhelst 2013).

Whilst in the Maiz 1998 case report MRSA was not eradicated after the 17-month treatment with daily continuous inhaled vancomycin, the authors did report improvements in lung function and symptom score in the child. The Vanderhelst 2013 study

reported a non-statistically significant trend in improvement of FEV1% in the 11 patients they studied, after successful eradication of MRSA. The largest cohort study (Dalbøge 2013) successfully eradicated *Staphylococcus aureus* from the sputum samples of the 65 patients they treated, and reported a statistically significant median (range) improvement in FEV1% predicted of 3.3% (−25% to 36%, p<0.0001). However, they did not differentiate between those patients who grew MSSA or those who grew MRSA from their sputum.

This is contradictory to two other studies, which reported no significant differences in lung function between participants who were successfully eradicated when compared to those who were not (Garske 2004; Solis 2003); however, this may be because the numbers were too small to detect a difference. The final two studies reported successful eradication of MRSA, Macfarlane 2007 (in 94% of patients) and Serisier 2004 (in one 28-year old), but did not report on lung function or patient clinical status during or following eradication.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently no published evidence from randomised controlled trials to support any one eradication regimen over another. While there are reports of successful eradication in those with CF, there is considerable uncertainty whether this is associated with patient benefit.

Implications for research

This review has highlighted the lack of evidence behind the present management of MRSA respiratory infections in CF and emphasizes the need for well-designed, adequately-powered trials with long-term follow-up in order to address this.

These will need to address the questions.

1. Does eradication of MRSA confer a favourable prognosis (see Types of outcome measures) for people with CF?
2. What is the optimal duration of treatment?
3. What is the most effective method of providing treatment (oral or intravenous or inhaled)?
4. Are there any pitfalls to treating MRSA aggressively (i.e. selection for other resistant pathogens, reduced patient tolerability)?

The published reports of the two ongoing studies identified are keenly awaited and the authors look forward to assessing the published data of these for inclusion into a future update of this review.

ACKNOWLEDGEMENTS

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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 study 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
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
Conway 1996	Not relevant participants - did not differentiate between organisms causing exacerbation leading to inclusion into the trial
Cooper 1985	Not relevant participants - trial of *P. aeruginosa* treatment.
Dalbøge 2013	An observational study. Not randomised.
Davis 1987	Pharmocokinetic study.
Degg 1996	Not a relevant intervention or relevant participants - study on long-term effects of gentamicin on hearing. Participants not selected on basis of microbial colonisation
Dodd 1997	Not a relevant intervention or relevant participants - testing differences in lung function relating to tonicity of nebulised colistin
Dodd 1998	Not a relevant intervention or relevant participants - a compliance study. No suitable control
Garske 2004	An observational study.
Geller 2004	Pharmocokinetic study.
Goldfarb 1986	Pharmocokinetic study.
Griffith 2008	Pharmocokinetic/tolerability study.
Gulliver 2003	Not a relevant intervention or relevant participants - testing whether nebulised IV tobramycin solution induced cough or bronchoconstriction or both
Heininger 1993	Not relevant participants - trial of *P. aeruginosa* treatment.
Hjelte 1988	Not relevant participants - investigated affect of home IV antibiotics for *P. aeruginosa* on quality of life.

(*Continued*)

Huang 1979	Not relevant participants - did not differentiate between organisms causing exacerbation leading to inclusion into trial
Huls 2000	Pharmocokinetic study.
Junge 2001	Not relevant participants - investigating risk of ototoxicity or cochlea damage in once daily versus 3-times daily IV tobramycin
Kapranov 1995	Not relevant participants - trial of *P. aeruginosa* treatment.
Keel 2011	Pharmocokinetic study.
Keller 2010	Pharmocokinetic study.
Knight 1979	Not relevant participants - trial of *P. aeruginosa* treatment.
Labiris 2004	Not a relevant intervention or relevant participants - objective was to determine whether preservative containing inhaled tobramycin causes airway inflammation
Loening -Bauke 1979	Not a relevant intervention - used cephalexin as prophylaxis
Macfarlane 2007	An observational study.
Maiz 1998	A case report of one 10-year old boy.
Nathanson 1985	Not relevant participants - trial of *P. aeruginosa* treatment.
Nolan 1982	Not a relevant intervention - prophylaxis rather than eradication
Pai 2006	Pharmocokinetic study.
Postnikov 2000	Not relevant participants - compared children with CF and aplastic anaemia
Postnikov 2001a	Not a relevant intervention or relevant participants - describes risk of quinolone arthropathy in children
Postnikov 2001b	Not a relevant intervention or relevant participants - investigated the effect on growth with the addition of ciprofloxacin to the treatment of children with CF
Ramstrom 2000	Not a relevant intervention - compared quality of life scores in patients who received pre-made infusion devices compared to those who reconstituted drugs themselves
Roberts 1993	Pharmocokinetic study.
Romano 1991	Not relevant participants - trial of *P. aeruginosa* treatment.
Rosenfeld 2006	Pharmocokinetic study.

(*Continued*)

Sahl 1992	Not relevant participants - MRSA not required for entry into study
Serisier 2004	A case report of one 28-year old man.
Shapera 1981	Not relevant participants - did not differentiate between MRSA and MSSA in inclusion criteria. Unclear how randomisation was achieved
Smith 1997	Pharmocokinetic study.
Solis 2003	Retrospective study.
Stutman 1987	Not relevant participants - pharmacokinetic study of *P. aeruginosa* treatment.
Vanderhelst 2013	An observational study. Not randomised.
Vitti 1975	Pharmocokinetic study.
Wood 1996	Not a relevant intervention - compared aminoglycoside toxicity in twice and 3-times daily dosing regimens

CF: cystic fibrosis
IV: intravenous
MRSA: meticillin-resistant *Staphylococcus aureus*
MSSA: meticillin-sensitive *Staphylococcus aureus*
P. aeruginosa: Pseudomonas aeruginosa

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

NCT01349192

Trial name or title	Early meticillin-resistant *Staphylococcus aureus* (MRSA) therapy in cystic fibrosis (CF) (STAR-Too).
Methods	Randomized, open-label, multicentre study comparing use of an eradication protocol to an observational group receiving the current standard of care, i.e. treatment for MRSA only with pulmonary exacerbations
Participants	Participants will include people ≥4 and ≤45 years with CF and new isolation of MRSA from their respiratory culture on a routine clinic visit. Estimated enrolment is 80
Interventions	**Eradication protocol**: 14-day oral rifampicin plus TMP-SMX or minocycline in people with contraindications to TMP-SMX **Observational group**: current standard of care, i.e. treatment for MRSA only with pulmonary exacerbations Drug: rifampin (adult dose: 300 mg twice daily for 14 days; paediatric dose: <40 kg: 15 mg/kg daily for 14 days divided every 12 hours). Drug: TMP-SMX (adult dose: 320/1600 orally twice daily for 14 days; paediatric dose: <40 kg: 8 mg/kg trimethoprim, >40 mg/kg sulfamethoxazole twice daily for 14 days). Drug: minocycline (only participants 8 years of age or older, who are not able to tolerate TMP/SMX or whose

NCT01349192 (*Continued*)

	screening MRSA is resistant to TMP/SMX, should be prescribed minocycline. Adult dose: 100 mg orally twice daily for 14 days. Paediatric dose: <50 kg: 2 mg/kg orally twice daily for 14 days not to exceed 200 mg per day). Drug: mupirocin (1 g 2% nasal ointment generously applied to each nostril using a cotton swab twice daily for 14 days). Drug: chlorhexidine gluconate oral rinse (0.12% chlorhexidine gluconate oral rinse twice daily for 14 days). Drug: 2% chlorhexidine solution wipes (whole body wash solution wipes once daily for the first 5 days). Behavioral: environmental decontamination (wipe down high-touch surfaces and medical equipment with surface disinfecting wipes daily for the first 21 days. Wash all linens and towels in hot water once weekly for 3 weeks)
Outcomes	**Primary outcome measure** 1. Proportion of participants in each arm with MRSA-negative respiratory cultures at day 28. **Secondary outcome measures** 1. Proportion of participants treated with oral, inhaled, and IV antibiotics over the 6-month study and number of days of use 2. Proportion of participants with a protocol-defined pulmonary exacerbation between baseline and day 28 who are treated with antibiotics active against MRSA
Starting date	April 2011.
Contact information	Marianne S Muhlebach, MD, University of North Carolina, Chapel Hill
Notes	Study closed for enrolment but some participants are still being actively followed up. Data analyses expected to begin in 2015

NCT01594827

Trial name or title	Persistent meticillin resistant Staphylococcus aureus eradication protocol (PMEP)
Methods	Randomised, placebo-controlled parallel trial. Duration 28 days with additional 3-month follow-up. Participants will be assigned in a 1:1 ratio to either treatment or control group
Participants	40 participants with persistent respiratory tract MRSA infection will be enrolled in this trial Inclusion criteria: 1. male or female $\geq$ 12 years of age; 2. confirmed diagnosis of CF based on the following criteria: positive sweat chloride > 60 mEq/liter (by pilocarpine iontophoresis) and/or a genotype with 2 identifiable mutations consistent with CF or abnormal NPD, and 1 or more clinical features consistent with the CF phenotype; 3. written informed consent (and assent when applicable) obtained from participant or participants's legal representative and ability for participant to comply with the requirements of the study; 4. 2 positive MRSA respiratory cultures in the last 2 years at least 6 months apart, plus a positive MRSA respiratory culture at screening visit and run-in (day 14) visit; 5. at least 50% of respiratory cultures from the time of the first MRSA culture (in the last 2 years) have been positive for MRSA; 6. FEV_1 > 30% of predicted normal for age, gender, and height at screening;

NCT01594827 (*Continued*)

	7. females of childbearing potential must agree to practice 1 highly effective method of birth control, including abstinence. Note: highly effective methods of birth control are those, alone or in combination, that result in a failure rate less than 1% per year when used consistently and correctly. Female participants who utilize hormonal contraceptives as a birth control method must have used the same method for at least 3 months before study dosing. If the participant is using a hormonal form of contraception, she will be required to also use barrier contraceptives as rifampin can affect the reliability of hormone therapy. Barrier contraceptives such as male condom or diaphragm are acceptable if used in combination with spermicides.
Interventions	**Treatment group**: 28-day course of inhaled vancomycin for inhalation (250 mg twice-a-day) plus oral rifampicin and oral TMP/SMX **Control group**: taste-matched inhaled placebo (sterile water) plus oral rifampicin and oral TMP/SMX In addition, both groups will receive oral rifampin, a second oral antibiotic (TMP-SMX or doxycycline, protocol determined), mupirocin intranasal cream and chlorhexidine body washes
Outcomes	**Primary objectives** 1. To determine the efficacy of an aggressive treatment protocol in eradicating persistent MRSA infection in individuals with CF 2. To determine the safety of an aggressive treatment protocol in eradicating persistent MRSA infection in individuals with CF **Secondary objectives** 1. To determine the efficacy of an aggressive treatment protocol in improving FEV_1, time to next exacerbation, and quality of life in individuals with CF and persistent MRSA infection 2. To determine if there is benefit to adding nebulized vancomycin to an aggressive oral antibiotic treatment protocol in eradicating persistent MRSA infection in individuals with CF
Starting date	Oct 2012.
Contact information	Michael Boyle, Associate Professor of Medicine, Johns Hopkins University
Notes	Currently actively recruiting. Estimated completion date: March 2015

NCT01746095

Trial name or title	Efficacy and safety study of AeroVanc for the treatment of persistent MRSA lung infection in cystic fibrosis patients
Methods	Randomised, double-blind, placebo-controlled trial. Duration 28 days with additional 56 days follow up. There will be two treatment cohorts in this study, each comprised of 40 randomized (1:1 active to placebo) participants. In Cohort 1, participants will be randomized to receive the 32 mg dose of AeroVanc twice daily or placebo twice daily. Prior to starting enrolment in Cohort 2, a safety evaluation will be carried out by the DMC based on treatment data from the first 20 participants in Cohort 1. Subject to the Sponsor's written communication of the DMC's opinion of acceptable safety, the dose for the active arm in Cohort 2 will be escalated to 64 mg twice daily. Optionally, the active arm for Cohort 2 may also be kept the same (32 mg twice daily), or reduced to 16 mg twice daily, depending on the outcome of the DMC's safety evaluation

Participants	87 participants with persistent respiratory tract MRSA infection have been enrolled onto this trial Inclusion criteria: 1. adults ≥18 years old (and the legally authorized representatives of children ≥12 but <18 years old). Children ≥12 but <18 years old: able to communicate with site personnel and to understand and voluntarily sign the assent form; 2. able and willing to comply with the protocol, including availability for all scheduled study visits; 3. have a confirmed diagnosis of CF, determined by having clinical features consistent with the CF phenotype, plus 1 of the following: a) positive sweat chloride test (value ≥60 mEq/L), or b) genotype with two mutations consistent with CF (i.e., a mutation in each of the CFTR genes); 4. be ≥12 years old at time of informed consent form or assent form signing; 5. have sputum culture positive for MRSA at screening, with at least 10,000 CFUs/mL of MRSA; 6. in addition to the screening sample, have at least 2 historical respiratory tract cultures (i.e., sputum and/or throat swab) positive for MRSA prior to screening and evidence that the MRSA lung infection has persisted for at least 6 months prior to screening; 7. have FEV_1 % predicted ≥30% and ≤100% normalized for age, gender, and height at screening; 8. evidence, defined as 1 or both of the following, that the persistent MRSA lung infection is suspected to be causing health consequences; have had at least 1 episode of acute pulmonary infection treated with non-maintenance antibiotics within 12 months from screening (initiation of treatment with intermittent inhaled anti-Pseudomonas therapy will not qualify as treatment with non-maintenance antibiotics); requires anti-MRSA treatment as part of a maintenance regimen to prevent pulmonary exacerbations or other respiratory symptoms; 9. be able to perform all the techniques necessary to use the AeroVanc inhaler and measure lung function; 10. be able to produce expectorated sputum samples or be able and willing to undergo standardized sputum induction; 11. agree not to smoke from screening through the end of the study; 12. females of child-bearing potential are eligible to participate in this study only if they are NOT pregnant or lactating, and if they are using a highly effective method of birth control; 13. participants with *P. aeruginosa* co-infection must either be stable on a regular suppression regimen of inhaled antibiotics or must be, in the opinion of the investigator, stable despite the lack of such treatment. Participants on a Cayston-based therapy must have received at least 2 cycles of Cayston prior to baseline (can be 2 consecutive months or 2 cycles over 4 months).
Interventions	**Treatment group:** A 28-day course of inhaled vancomycin (AeroVanc) starting at 32 mg twice per day, and either (a) increased (64 mg twice per day), (b) kept the same (32 mg twice per day), or (c) reduced (16 mg twice per day) pending initial safety evaluation **Control group:** A 28-day course of placebo inhalation powder.
Outcomes	**Primary outcome measure** 1. Change from baseline at Day 29 of the dosing period (start of AeroVanc/Placebo administration is considered Day 1 of the dosing period) in the number of MRSA CFUs in sputum culture **Secondary outcome measures** 1. Change from baseline in each pulmonary function test. 2. Change from baseline in Cystic Fibrosis Respiratory Symptom Diary scores 3. Change from baseline in MRSA sputum density. 4. Time from start of dosing to first administration of other antimicrobial medications (oral, intravenous and/or inhaled) due to respiratory symptoms 5. Time from start of dosing to exacerbation of signs/symptoms (Fuchs criteria) 6. Change from baseline in high sensitivity C-reactive protein and blood neutrophils

NCT01746095 (*Continued*)

Starting date	March 2013.
Contact information	Elliott Dasenbrook, MD. Case Western Reserve University School of Medicine and Rainbow Babies and Children's Hospital
Notes	Study completed November 2014. No results posted as of 14th December 2014

CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
CFU: colony forming unit
DMC: Data Monitoring Committee
FEV_1: forced expiratory volume at one second
MRSA: meticillin-resistant *Staphylococcus aureus*
P. aeruginosa : *Pseudomonas aeruginosa*
NPD: nasal potential difference
TMP-SMX: trimethoprim/sulfamethoxazole

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Search strategy for MEDLINE (1950 - December 2014) and Embase (1980 - December 2014)

1	Embase, MEDLINE	(methicillin AND resistant AND staphylococcus AND aureus OR MRSA OR methicillin AND resistant AND staphylococcus AND aureus OR methicillin AND staphylococcus).ti,ab	40457	Apply Limits
2	Embase, MEDLINE	(cystic AND fibrosis).ti,ab	68893	Apply Limits
3	Embase, MEDLINE	(eradication OR eradica*).ti,ab	86661	Apply Limits
4	Embase, MEDLINE	1 AND 2 AND 3	38	Apply Limits

WHAT'S NEW

Last assessed as up-to-date: 18 February 2015.

Date	Event	Description
18 February 2015	New citation required but conclusions have not changed	Given that no new data have been added to this review, our conclusions remain the same
18 February 2015	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register identified no new studies to be included in this review A search of PUBMED, Embase and MEDLINE identified a further three studies, none of which were eligible for inclusion in the analysis (Dalbøge 2013; Serisier 2004; Vanderhelst 2013). A search of the ongoing trials registers (www.clinicaltrials.gov; www.isrctn.org) identified one further ongoing study, which has been listed in the review (NCT01746095).

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO WILL UNDERTAKE THE TASK?
Protocol stage: draft the protocol	David Lo
Review stage: select which trials to include (2 + 1 arbiter)	David Lo, Matthew Hurley, Marianne Muhlebach, Alan Smyth
Review stage: extract data from trials (2 people)	David Lo, Matthew Hurley
Review stage: enter data into RevMan	David Lo
Review stage: carry out the analysis	David Lo, Matthew Hurley
Review stage: interpret the analysis	David Lo, Matthew Hurley, Marianne Muhlebach, Alan Smyth
Review stage: draft the final review	David Lo, Matthew Hurley
Update stage: update the review	David Lo

DECLARATIONS OF INTEREST

David Lo and Matthew Hurley: none known.

Marianne Muhlebach is one of the principle investigators for a randomised controlled study evaluating early treatment of MRSA; this study is currently in progress (NCT01349192).

Alan Smyth is the Co-ordinating Editor of the Cochrane Cystic Fibrosis and Genetic Disorders Group and declares relevant activities of: membership of a REMPEX steering committee; consultancies for Novartis, Biocontrol and Rempex Pharma (both make aerosolised antibiotics which are active against some strains of *Staphylococcus aureus*); and also a lecture paid for by Chiesi Pharma.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 2015 update we have changed the spelling of 'methicillin' to 'meticillin' in line with the change in the international non-proprietary name (although we are aware that in some parts of the world the drug is still known as methicillin).

INDEX TERMS

Medical Subject Headings (MeSH)

*Methicillin-Resistant Staphylococcus aureus; Cystic Fibrosis [*microbiology]; Staphylococcal Infections [*prevention & control]

MeSH check words

Humans