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Duration of intravenous antibiotic therapy in people with cystic fibrosis (Review)

Plummer A, Wildman M, Gleeson T

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[Intervention Review]

Duration of intravenous antibiotic therapy in people with cystic fibrosis

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ABSTRACT

Background

Respiratory disease is the major cause of mortality and morbidity in cystic fibrosis. Life expectancy of people with cystic fibrosis has increased dramatically in the last 40 years. One of the major reasons for this increase is the mounting use of antibiotics to treat chest exacerbations caused by bacterial infections. The optimal duration of intravenous antibiotic therapy is not clearly defined. Individuals usually receive intravenous antibiotics for 14 days, but treatment may range from 10 to 21 days. A shorter duration of antibiotic treatment risks inadequate clearance of infection which could lead to further lung damage. Prolonged courses of intravenous antibiotics are expensive and inconvenient and the incidence of allergic reactions to antibiotics also increases with prolonged courses. The use of aminoglycosides requires frequent monitoring to avoid some of their side effects. However, some organisms which infect people with cystic fibrosis are known to be multi-resistant to antibiotics, and may require a longer course of treatment. This is an update of previously published reviews.

Objectives

To assess the optimal duration of intravenous antibiotic therapy for treating chest exacerbations in people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises references identified from comprehensive electronic database searches, handsearches of relevant journals, abstract books and conference proceedings.

Most recent search of the Group's Cystic Fibrosis Trials Register: 05 May 2016.

Selection criteria

Randomised and quasi-randomised controlled trials comparing different durations of intravenous antibiotic courses for acute respiratory exacerbations in people with CF, either with the same drugs at the same dosage, the same drugs at a different dosage or frequency or different antibiotics altogether, including studies with additional therapeutic agents.

Data collection and analysis

No eligible trials were identified.

Main results

No eligible trials were identified.

Authors' conclusions

There are no clear guidelines on the optimum duration of intravenous antibiotic treatment. Duration of treatment is currently based on unit policies and response to treatment. Shorter duration of treatment should improve quality of life and compliance; result in a reduced incidence of drug reactions; and be less costly. However, this may not be sufficient to clear a chest infection and may result in an early recurrence of an exacerbation. This systematic review identifies the need for a multicentre, randomised controlled trial comparing different durations of intravenous antibiotic treatment as it has important clinical and financial implications.

PLAIN LANGUAGE SUMMARY

Length of time needed for antibiotic treatment given directly into the blood stream to clear acute chest infections in people with cystic fibrosis

Review question

We reviewed the evidence about how long intravenous antibiotic treatment (antibiotics given directly into the blood stream) is needed to clear flare ups of chest symptoms in people with cystic fibrosis.

Background

Flare ups of symptoms (exacerbations) in people with cystic fibrosis are treated aggressively to prevent further damage to the lungs. This practice has led to better survival rates for people with cystic fibrosis in recent years. However, there are no clear guidelines on how long treatment with intravenous antibiotics should be to treat these flare ups. Different centres tend to use different treatment regimens. Most centres use 10 or 14 days, extending this to 21 days if there is no improvement in a person's symptoms. This is an update of previously published reviews.

Search date

The evidence is current to: 05 May 2016.

Study characteristics

We could not find any studies comparing 10 days treatment with 14 days or longer treatment.

Key results

A shorter duration of treatment may be better as these courses of treatment are easier for people to complete. They are also less expensive and cause fewer drug reactions than longer treatments. However, it is not clear if shorter treatment is enough to treat infections adequately. It is also not clear whether shorter treatment results in early recurrence or increased frequency of chest infections. Further research is needed to find the best duration of treatment for exacerbations.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive genetic disorder in Caucasians (Kosorok 1996). Respiratory disease is the major cause of mortality and morbidity in CF (Penketh 1987). About 40 years ago, most people with CF died in their first decade of life. With advances in treatment, life expectancy has increased dramatically since then from a median

of two years to a projected median survival of over 50 years of age (Dodge 2007). One of the major reasons for this increase in survival is the mounting use of antibiotics to treat chest exacerbations caused by bacterial infections.

The abnormal CF gene causes a combination of increased sodium and defective chloride absorption across the airway epithelium, which in turn causes dehydration and leads to a build up of thick sticky mucus. This accumulates in the lungs and causes chronic pulmonary infections and bronchiectasis. In people with CF, bacterial pathogens are the main causes of respiratory exacerbations (Petersen 1981; Wat 2003).

In small children, *Staphylococcus aureus* (*S. aureus*) and *Haemophilus influenzae* (*H. influenzae*) are the most common organisms isolated and thought to be responsible for chest exacerbations, but pneumococci and sometimes Enterobacteriaceae are also isolated. In older children and adults, the major pathogen is *Pseudomonas aeruginosa* (*P. aeruginosa*), although the other organisms mentioned above can also be responsible and, in some centres *Burkholderia cepacia* (*B. cepacia)* too (Hodson 2000a).

At birth the lungs of infants with CF are normal, but shortly thereafter many become infected with bacteria (Accurso 1997). Endobronchial infection commonly occurs within the first one to two years of life (Armstrong 1995). The most common organism isolated from the sputum of adults is *P. aeruginosa* (Horre 2004), with traditionally 80% of people with CF being infected by 18 years of age (CF Foundation 2001; Hodson 2000b). This is no longer the case and chronic colonisation with *P. aeruginosa* can be prevented or delayed by segregation and aggressive eradication treatment of first isolates (Hansen 2008; Stuart 2010). Prevalence data from the UK indicates a rate of chronic *P. aeruginosa* infection of 45% in 16 to 19 year olds, riding to a peak of 67% in 28 to 31 year olds (CF Trust 2009). Chronic infection with *P. aeruginosa* is however associated with a more rapid decline in lung function (Emerson 2002; Schaedel 2002).

Most people with CF are initially infected with non-mucoid *P. aeruginosa*, which is relatively sensitive to antibiotics, but after a period of time it changes to a mucoid state (Starner 2005). Early acquisition of mucoid *P. aeruginosa* was associated with a four-fold greater decrease in cumulative survival (Demko 1995). Mucoid *P. aeruginosa* is much more difficult to treat and eradicate because it adopts a defensive mode of growth that leads to creation of a surrounding biofilm (Hentzer 2001; Høiby 2000). Biofilms are communities of bacteria enclosed in a self-produced polysaccharide matrix and which are adherent to a surface. The biofilm protects *P. aeruginosa* from normal host defences and antibiotics. In addition, bacterial adherence to mucus is increased in CF which also contributes to difficulties in clearing it from the airways (Donaldson 2003).

Description of the intervention

At the time of initial infection, the majority of *P. aeruginosa* isolates are susceptible to commonly used antibiotics but, as individuals are exposed to repeated courses of antimicrobial therapies, they often develop drug resistance (Gilligan 1999). Multi-resistant *P. aeruginosa* is associated with more severe lung disease, more rapid decline in FEV_1 and progression to end-stage lung disease (Lechtzin 2006). People with CF who are infected with multi-resistant *P. aeruginosa* require longer duration of intravenous antibiotics, more courses of intravenous antibiotics per year and more clinic visits (Lechtzin 2006). Certain highly transmissible *P. aeruginosa* strains, which can be detected by genomic fingerprinting, are also known to be multi-resistant and have a greater requirement for intravenous antibiotics than those harbouring unique strains (Jones 2002). These epidemic, multi-resistant strains can spread among people with CF with significant resource implications (Cheng 1996; Edenborough 2004; Jones 2001). Other organisms which infect people with CF and are known to be multi-resistant to antibiotics are *B. cepacia* complex, *Stenotrophomonas maltophilia (S. maltophilia)* and *Achromobacter (Alkaligines) xyloxidans* (Elborn 2004). Infection with multi-resistant organisms is associated with more severe respiratory exacerbations requiring a longer duration of intravenous antibiotics (Frangolias 1999; Lechtzin 2006).

Intravenous antibiotics are given either as home intravenous antibiotic treatment (HIVAT) or in hospital. For the treatment of chest exacerbations, the choice of intravenous antibiotics is generally based on recent culture results of airway secretions. In infections caused by *P. aeruginosa*, a combination of aminoglycoside and beta lactam is preferred as it enhances the activity against target organisms (synergy) and decreases the risk of antibiotic resistance developing (Cheng 1996).

How the intervention might work

Deciding on an optimal combination of antibiotic regimens depends on many factors, namely the type of organisms, antibiotic sensitivity, allergies, previous response to treatment and local policies. A good response to treatment can be expected if a suitable antibiotic combination is chosen.

The duration of a course of intravenous therapy to treat chest exacerbations varies but these are frequently between 10 and 21 days of antibiotics (CF Trust 2009; Doring 2000; Döring 2012; Gibson 2003; Hodson 2000a). The optimal duration of intravenous antibiotic therapy is not clearly defined (Rosenberg 1993). Response to therapy (as reflected by improved pulmonary function, oxygen saturation returning to pre-exacerbation levels, levelling off of weight loss, normalisation or significant falls in inflammatory markers, decreased bacterial density in sputum, improved well-being and clinical symptomatology scores) may be used to guide the optimal duration of intravenous antibiotic therapy (CF Trust 2009; Doring 2000; Döring 2012; Hodson 2000a; Ramsey 1996).

Individuals are usually commenced on a 10- to 14-day course of intravenous antibiotics (CF Trust 2009; Doring 2000; Döring 2012). This may be extended in people with severe exacerbations and incomplete recovery (Doring 2000; Döring 2012). However a consensus of opinion states that intravenous antibiotics should not be extended more than three weeks, except under very special circumstances and that patients with multi-drug resistant *P. aeruginosa* may require therapy (Döring 2012).Some studies also mention 10 days (CF Trust 2009; Doring 2000; Hodson 2000b; McLaughlin 1983) and 21 days (Gibson 2003; Ramsey 1996) as the duration required to treat chest exacerbations. With a shorter duration of antibiotic treatment there is a risk of inadequate clearance of infection which could lead to further lung damage. Prolonged courses of intravenous antibiotics are expensive and inconvenient to individuals. The incidence of allergic reactions to antibiotics also increases with prolonged courses (Koch 1991; Parmar 2005). Moreover, the use of aminoglycosides requires frequent monitoring of antibiotic levels to avoid some of their side effects namely, ototoxicity and nephrotoxicity (Hodson 2000b).

Why it is important to do this review

The aim of this review is to assess the available evidence in order to establish the optimal duration of intravenous antibiotic therapy for treating a chest exacerbation in people with CF. This is an update of previously published reviews (Plummer 2011; Plummer 2013).

OBJECTIVES

To assess the optimal duration of intravenous antibiotic therapy for treating chest exacerbations in people with cystic fibrosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-randomised controlled trials.

Types of participants

People with CF, diagnosed clinically and by sweat or genetic testing, of all ages and all degrees of disease severity and who are being treated with intravenous antibiotics for a chest exacerbation.

We will require all studies to clearly state how they will define a chest exacerbation. We will regard as important or as a minimum, according to criteria published by the 1994 Cystic Fibrosis Foundation Microbiology and Infectious Disease Consensus Conference (CF Foundation 1994), the presence of at least three of the following eleven new findings or changes in clinical status when compared to the most recent baseline visit:

1. increased cough;
2. increased sputum production, change in appearance of expectorated sputum, or both;
3. fever (greater or equal to 38°C for at least four hours in a 24-hour period) on more than one occasion in the previous week;
4. weight loss greater than or equal to 1 kg or 5% of bodyweight associated with anorexia and decreased dietary intake;
5. school or work absenteeism (due to illness) in the previous week;
6. increased respiratory rate, increased work of breathing, or both;
7. new finding on chest examination (e.g. rales, wheezing, crackles);
8. decreased exercise tolerance;
9. decrease in FEV_1 of greater than or equal to 10% from previous baseline study within past three months;
10. decrease in haemoglobin saturation (as measured by oximetry) from baseline value within past three months of greater than or equal to 10%;
11. new finding on chest radiograph.

For paediatric chest exacerbations, the presence of three or more of the following characteristics will be used to define a chest exacerbation:

1. in children under six years of age - new crackles, increased cough frequency, decline in weight and impression of increased sputum production;
2. in children six years or over - relative decrease in per cent predicted FEV_1, increased cough frequency, new crackles and haemoptysis (Rabin 2004).

For the purpose of this study we will exclude people with CF who are treated electively with intravenous antibiotics and eradication regimens and only consider people with CF being treated for acute chest exacerbations.

Types of interventions

Comparison of different durations of intravenous antibiotic courses, which can either be the same drugs at the same dosage, the same drugs at a different dosage or frequency or different antibiotics altogether. We will not exclude studies in which there are additional therapeutic agents included e.g. prednisolone, azithromycin, dornase alpha or nebulised tobramycin or colistin.

Types of outcome measures

Short-term outcomes

Primary outcomes

1. Lung function (absolute change or percentage change compared to baseline values or both)
   i) forced expiratory volume at one second (FEV_1) (measured in L/min or % predicted)
   ii) forced vital capacity (FVC) (measured in L/min or % predicted)
   iii) expiratory flow from 25% to 75% of vital capacity ($FEF_{25–75}$)
2. Change in sputum bacteriology (quantitative e.g. colony-forming units per ml, or qualitative e.g. type of bacteria, or both)
3. Adverse effects (e.g. allergic reactions, candidal infections)

Secondary outcomes

1. Quality of life (measured by health status questionnaires, if available)
2. Change in nutritional status (absolute change or percentage change or both compared with baseline values) - *Post hoc change:* ideally, the following measures should be age-adjusted in paediatric participants
   i) weight
   ii) height
   iii) body mass index (BMI)
3. Time to next exacerbation
4. Change in inflammatory markers
   i) measured in the sputum
   ii) measured in the blood
5. Cost
6. Treatment failure (defined as need to change to a different course of antibiotics because of clinical deterioration of the participant)

Long-term outcomes

Primary outcomes

1. Frequency of exacerbations of chest disease
2. Lung function (absolute change or percentage change compared to baseline values or both)
   i) FEV_1 (measured in L/min or % predicted)
   ii) FVC (measured in L/min or % predicted)
   iii) $FEF_{25–75}$
3. Development of antibiotic-resistant strains
   i) *Pseudomonas aeruginosa*
   ii) other organisms

Secondary outcomes

1. Adverse effects (e.g. decline in renal function)
2. Number of intravenous antibiotic courses since study
3. Quality of life (measured by health status questionnaires, if available)
4. Cost

Search methods for identification of studies

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (intravenous OR not stated).

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

Date of most recent search of the Cystic Fibrosis Trials Register: 05 May 2016.

Data collection and analysis

We were unable to identify any trials eligible for inclusion in this review. If we identify relevant trials for a future update we plan to undertake the following.

Selection of studies

Two authors (AP, MW or TG) will independently apply the inclusion criteria to all potential trials. We will perform this without blinding. Any discrepancy that occurs in the trial selection will be resolved by discussion.

Data extraction and management

Two authors (AP, MW) will independently extract the data (using a customised data extraction form) and assess the methodological quality of the selected trials. Any discrepancy that occurs in the trial selection will be resolved by discussion.

For short-term outcomes, we plan to measure outcomes at less than a week, one to two weeks, more than two weeks to three weeks, more than three weeks to four weeks. We will also consider additional follow-up data recorded at other time periods.
Long-term outcomes will be measured from six months following the end of the course of antibiotics in the study. For long-term outcomes, we plan to measure outcomes at one month, up to three months, up to six months, up to twelve months and then annually thereafter. If outcome data are recorded at other time periods we will consider examining these as well.

Assessment of risk of bias in included studies

The risk of bias will be assessed using The Cochrane Collaboration "risk of bias" tool (Higgins 2011), The risk of bias will be considered for the following sections.

1. Sequence generation: a detailed description of the method of used to generate the sequence allocation will be obtained and evaluated for the ability to produce bias.
2. Allocation concealment: a detailed description of the methods used will be obtained. The ability to predict the randomisation of the current or future patients will be assessed.
3. Blinding: as any eligible studies will be randomised controlled trials of duration of intravenous antibiotics the patients and clinicians will be aware of the duration of treatment unless placebo medicines are given for the additional days. Given the nature of the drugs and the effects it is likely that these could be detected by patients and healthcare professionals. The ability of any methods used to reduce bias will be considered in the following groups, patient, clinician and outcome assessor.
4. Incomplete outcome data: we will review incomplete data for each main outcome for both attrition and exclusions. The studies will be assessed for an intention-to-treat analysis.
5. Selective reporting: the outcomes will be reviewed for completeness of presentation. Any suggestions of selective reporting will be followed up with the authors.
6. Other potential sources of bias: any other potential sources of bias will be considered according to the questions the study is answering.

Measures of treatment effect

For binary outcome measures, in order to allow an intention-to-treat analysis, we will seek data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the individual was later thought to be ineligible or otherwise excluded from treatment or follow up. We aim to calculate a pooled estimate of the treatment effect for each outcome across studies using relative risk where appropriate. For continuous outcomes, we plan to record either mean relative change from baseline for each group or mean post-treatment or intervention values and standard deviation. If standard errors are reported, and where possible, these will be converted to standard deviations. We will calculate a pooled estimate of treatment effect by calculating the weighted mean difference.
For any time-to-event outcomes included in the review, we plan to obtain a mixture of logrank and Cox model estimates from the trials; we will combine all results using the generic inverse variance method since we will be able to convert the logrank estimates into log hazard ratios and standard errors as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
We will analyse longitudinal data using the most appropriate method available.

Unit of analysis issues

Ideally, when conducting a meta-analysis combining results from cross-over trials we will use the inverse variance methods that are recommended by Elbourne (Elbourne 2002). However, if there are restrictions on the data available, we may only be able to either use the first arm data only or to treat the cross-over trials as if they are parallel trials. Elbourne says that this approach will produce conservative results as it does not take into account within-patient correlation (Elbourne 2002). Also each participant will appear in both the treatment and control group, so the two groups will not be independent.

Dealing with missing data

We will contact the authors of the original studies for data for any missing individuals, outcomes or summary data. We plan to describe the implications of any missing data in detail and include this in the discussion. We may impute missing standard deviations according to the methodology described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will collect any outcomes not available and report these in a risk of bias table. We plan to conduct an intention-to-treat analysis by contacting all authors for missing data. If there are large amounts of missing data which we can not impute with more than minimal assumptions, we will perform an available case analysis.

Assessment of heterogeneity

We plan to quantify the impact of statistical and clinical heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the studies' results (Higgins 2003). This measure (I^2) describes the percentage of total variation across studies that are due to heterogeneity above that due to chance. The values of I^2 lie between 0% and 100%, and a simplified categorisation of heterogeneity that we plan to use is of listed below (Higgins 2011) :

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

Assessment of reporting biases

We will attempt to assess whether our review is subject to publication bias by using a funnel plot. If asymmetry is detected, causes other than publication bias will be explored.

Data synthesis

If no significant heterogeneity is identified, we will compute pooled estimates of the treatment effect for each outcome under a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If we find significant heterogeneity, we will investigate the possible causes of this further by exploring the impact of methodological quality and condition of the individuals (i.e. severity of disease, type of treatment, e.g. single or combined treatment) using subgroup analysis.

We will perform a subgroup analysis based on bacteriology - chronically infected with *P. aeruginosa* only, *P. aeruginosa* and other organisms (excluding *B. cepacia*), *B. cepacia* (with or without co-infection with other organisms) and non-*P. aeruginosa* organisms (excluding *B. cepacia*). Chronic infection is defined as at least two positive sputum cultures in the previous six months (CF Trust 2009).

We will compare duration of treatment used in HIVAT and hospital treatment separately. However, comparison of home versus hospital intravenous antibiotic treatment is the subject of another Cochrane review (Balaguer 2008) and this comparison is included here only as part of subgroup analysis to assess its impact on duration of treatment.

We will also compare duration of treatment based on age separately in three groups: under six years of age; between six and sixteen years of age; and over sixteen years of age.

Sensitivity analysis

We plan to perform a sensitivity analysis based on the methodological quality of the trials, including and excluding quasi-randomised trials.

RESULTS

Description of studies

No trials were identified which were eligible for inclusion in this review. A total of 227 papers were obtained from the Group's Cystic Fibrosis Trials Register. Out of these, only 84 papers involved treatment of chest exacerbations with intravenous antibiotics. The rest of the trials were excluded because they involved oral or nebulised antibiotics or were pharmacokinetic studies, studies concerning method of delivery or without any clinical outcome measures. Of the 84 papers that were reviewed, none of these RCTs compared different durations of antibiotic courses and are therefore not eligible for inclusion in this review. We have listed 12 trials (19 references) under 'Excluded studies' and the reasons for exclusion are provided in the tables 'Characteristics of excluded studies'.

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

Cystic fibrosis is a life-limiting disease. While every effort needs to be focused on treating chest infections aggressively, there have been no clear guidelines on how long the optimum duration of intravenous antibiotics should be. Most studies show chest exacerbations are treated for 14 days as a routine (Aaron 2005; Burkhardt 2006; Hoogkamp 1983; Hyatt 1981; Smyth 2005; Vic 1998); however, there are studies which show 10 days are sufficient (Beaudry 1980; Master 2001; McLaughlin 1983; Penketh 1983; Penketh 1984). A study by Mendelman found 21 days to be more effective in treating chest exacerbations (Mendelman 1985). None of these studies are RCTs which compare different durations of antibiotic courses and are therefore not eligible to be included in the Results section of this review. There are no clear reasons for choosing 14 days or 21 days as the optimum duration, besides the assumption that longer treatment may clear the infection more thoroughly. Moreover, not all chest exacerbations are due to the usual bacteria known to infect the lungs of people with CF. Viruses, atypical bacteria and fungi are also implicated in causing exacerbations (Olesen 2006). Physiotherapy and bronchodilators on their own, sometimes, have the same effect as intravenous antibiotics in treating chest exacerbations (Gold 1987). As it is difficult to clinically distinguish bacterial and viral exacerbations, clinicians usually err on the side of treating them with antibiotics.

In most adults and adolescents with CF, eradication of the infecting bacterial organism is almost impossible as infections tend to be chronic and ineradicable. Therefore, extending duration of antibiotic therapy would not be expected to result in clearance of infection. In contrast to acute infections associated with other

diseases, the duration of antibiotic therapy for CF exacerbations should probably be guided based on improvement in clinical status of the affected individual rather than based on attempts at rendering the airways sterile of bacteria.

We did not find any RCTs comparing different treatment durations. Reducing the treatment duration to 10 days may have significant benefits; improved quality of life, improved compliance, less incidence of drug reactions and lower cost. However, it is uncertain if this duration of 10 days is sufficient to clear a chest infection and does not result in an early recurrence of next exacerbation. Moreover, multi-resistant organisms may require longer duration to treat them effectively.

adequately-powered, multicentre randomised controlled trial to assess the optimum duration of intravenous antibiotic therapy to treat chest exacerbations, an issue which has important clinical and financial implications. This type of study could be done by randomising participants to receive either 7 days, 10 days, 14 days or 21 days of intravenous antibiotics and comparing outcome measures at these various end points. Long-term follow up is needed to look at the time to next exacerbation, frequency of chest exacerbations and development of antibiotic-resistant strains. Outcome measures, such as pulmonary function tests, time to next exacerbation and improvement in quality of life scores should be clearly stated and multicentre trials should be co-ordinated so that maximum power is available to achieve a clear result.

AUTHORS' CONCLUSIONS

Implications for practice

There are no published data to recommend the optimum duration of intravenous antibiotic therapy for treating a chest exacerbation. Duration of treatment is currently decided based on unit policies and the individual's response to treatment and we have found no evidence to change this practice.

Implications for research

This systematic review has identified the need for a well-designed,

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2010 - the current authors (AP and MW) would like to thank Dr Bryan Fernandes for his input into previous versions of this review.

REFERENCES

References to studies excluded from this review

Adeboyeku 2011 *{published data only}*

Adeboyeku D, Jones AL, Hodson ME. Twice vs three-times daily antibiotics in the treatment of pulmonary exacerbations of cystic fibrosis. *Journal of Cystic Fibrosis* 2011;**10**(1):25–30. [CFGD Register: PI250;]

Blumer 2005 *{published data only}*

Blumer JL, Minkwitz M, Saiman L, San Gabriel P, Iaconis J, Melnick D. Meropenem (MEM) compared with ceftazidime (CAZ) in combination with tobramycin (TOB) for treatment of acute pulmonary exacerbations (APE) in patients with cystic fibrosis (CF) infected with Pseudomonas aeruginosa (PA) or burkholderia cepacia (BC) [abstract]. *Pediatric Pulmonology* 2003;**Suppl 25**:294. [CFGD Register: PI179a;]

* Blumer JL, Saiman L, Konstan MW, Melnick D. The efficacy and safety of meropenem and tobramycin vs ceftazidime and tobramycin in the treatment of acute pulmonary exacerbations in patients with cystic fibrosis. *Chest* 2005;**128**(4):2336–46. [CFGD Register: PI179b;]

Hjelte 1988 *{published data only}*

Hjelte L, Widen B, Malmborg AS, Freyschuss U, Strandvik B. Intravenous administration of antibiotics at home in patients with cystic fibrosis improves quality of life [Intravenos antibiotikabehandling i hemmet vid cystisk fibros ger okad livskvalitet]. *Lakartidningen* 1988;**85**(18): 1614–7. [CFGD Register: PI206;]

Hubert 2009 *{published data only}*

* Hubert D, Le Roux E, Lavrut T, Wallaert B, Scheid P, Manach D, et al. Continuous versus intermittent infusions of ceftazidime for treating exacerbation of cystic fibrosis. *Antimicrobial Agents and Chemotherapy* 2009;**53**(9):3650–6. [CFGD Register: PI180b;]

Hubert D, Wallaert B, Scheid P, Ramel S, Grenet D, Sermet-Gaudelus I, et al. Continuous infusion versus intermittent administration of ceftazidime in cystic fibrosis patients [abstract]. *Pediatric Pulmonology* 2003;**Suppl 25**: 294. [CFGD Register: PI180a;]

Kapranov 1995 *{published data only}*

Kapranov NI, Belousov YB, Kashyrskaya NY, Smirnova EY. Quinoline therapy in children with cystic fibrosis [abstract]. Proceedings of 20th European Cystic Fibrosis Conference; 1995 June 18-21; Brussels, Belgium. 1995:P19. [CFGD Register: PI104;]

Keel 2011 *{published data only}*

Keel RA, Schaeftlein A, Kloft C, Pope JS, Knauft RF,

Muhlebach M, et al. Pharmacokinetics of intravenous and oral linezolid in adults with cystic fibrosis. *Antimicrobial Agents and Chemotherapy* 2011;**55**(7):3393–8. [CFGD Register: PI251;]

Kenny 2009 ***{published data only}***

Kenny S, Hall V, Goldsmith C, Moore J, Rendall JC, Elborn JS. Eradication of Pseudomonas aeruginosa in adults with CF [abstract]. *Journal of Cystic Fibrosis* 2009;**8**(Suppl 2):S39, Abstract no: 158. [CFGD Register: PI229;]

Knight 1979 ***{published data only}***

Knight RK, Batten JC, Mearns M. A double blind trial of cephalexin in cystic fibrosis patients with pseudomonas in the sputum [abstract]. Proceedings of 9th Meeting European Working Group for Cystic Fibrosis; 1979 June 12-13; Noordwijkerhout, The Netherlands. 1979:52. [CFGD Register: PI124;]

Latzin 2008 ***{published data only}***

Latzin P, Fehling M, Bauernfeind A, Reinhardt D, Kappler M, Griese M. Efficacy and safety of intravenous meropenem and tobramycin versus ceftazidime and tobramycin in cystic fibrosis. *Journal of Cystic Fibrosis* 2008;**7**(2):142–6. [CFGD Register: PI209; MEDLINE: 87210211]

Postnikov 2007 ***{published data only}***

Postnikov SS, Semykin SY, Polikarpova SV, Dubovik LG, Gracheva LA, Sagatelyan RM. A prospective trial on the efficacy and tolerability of twice-daily dosing (TDD) versus once-daily dosing (ODD) amikacin in cystic fibrosis patients [abstract]. *Journal of Cystic Fibrosis* 2007;**6**(Suppl 1):S34. [CFGD Register: PI204;]

Riethmueller 2009 ***{published data only}***

* Riethmueller J, Ballmann M, Schroeter TW, Franke P, von Butler R, Claass A, et al. Tobramycin once- vs thrice-daily for elective intravenous antipseudomonal therapy in pediatric cystic fibrosis patients. *Infection* 2009;**37**(5): 424–31. [CFGD Register: PI154f;]

Riethmueller J, Busch A, Franke P, Ziebach R, von Butler R, Stern M. Pharmacodynamic variation of intravenous antibiotic treatment with ceftazidime and tobramycin in CF-patients is equally effective [abstract]. Proceedings of 13th international cystic fibrosis congress; 2000 June 4-8; Stockholm, Sweden. 2000:166. [CFGD Register: PI154a;]

Riethmueller J, Franke P, Schroeter TW, Claass A, Busch A, Ziebach R, et al. Optimised intravenous antibiotic treatment with ceftazidime (thrice daily vs continuous) and tobramycin (thrice vs once daily) in CF patients [abstract]. Proceedings of 24th European cystic fibrosis conference; 2001 June 6-9; Vienna, Austria. 2001:P192. [CFGD Register: PI154b;]

Riethmueller J, Junge S, Schroeter TW, Kuemmerer K, Franke P, Ballmann M, et al. Continuous vs thrice-daily ceftazidime for elective intravenous antipseudomonal therapy in cystic fibrosis. *Infection* 2009;**37**(5):418–23. [CFGD Register: PI154e;]

Schroeter T, Eggert P, Riethmueller J, Stern M, Claass A. Acute-phase nephrotoxicity of tobramycin in CF patients: A prospective randomized trial of once-versus thrice-daily dosing [abstract]. *Pediatric Pulmonology* 2002;**Suppl 24**: 289. [CFGD Register: PI154d;]

Schroeter TW, Eggert P, Riethmueller J, Stern M, Claass A. A prospective randomized trial on the nephrotoxicity of thrice-daily versus once-daily tobramycin in cystic fibrosis patients [abstract]. Proceedings of 24th European cystic fibrosis conference; 2001 June 6-9; Vienna, Austria. 2001: P190. [CFGD Register: PI154a;]

Semykin 2010 ***{published data only}***

Semykin SY, Polikarpova SV, Dubovik LG, Kashirskaya NY. Efficiency of the inhalational tobramycin therapy in complex antibacterial therapy of lung exacerbation in cystic fibrosis children with chronic pseudomonas aeruginosa infection [abstract]. *Journal of Cystic Fibrosis* 2010;**9 Supplement 1**:S55, Abstract no: 214. [CFGD Register: PI246;]

Additional references

Aaron 2005

Aaron SD, Vandemheen KL, Ferris W, Fergusson D, Tullis E, Haase D, et al. Combination antibiotic susceptibility testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. *Lancet* 2005;**366**(9484):463–71.

Accurso 1997

Accurso FJ. Early pulmonary disease in cystic fibrosis. *Current Opinion in Pulmonary Medicine* 1997;**3**(6):400–3.

Armstrong 1995

Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995;**310**(6994):1571–2.

Balaguer 2008

Balaguer A, González de Dios J. Home intravenous antibiotics for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD001917.pub2]

Beaudry 1980

Beaudry PH, Marks MI, McDougall D, Desmond K, Rangel R. Is anti-Pseudomonas therapy warranted in acute respiratory exacerbations in children with cystic fibrosis?. *Journal of Pediatrics* 1980;**97**(1):144–7.

Burkhardt 2006

Burkhardt O, Lehmann C, Madabushi R, Kumar V, Derendorf H, Welte T. Once-daily tobramycin in cystic fibrosis: better for clinical outcome than thrice-daily tobramycin but more resistance development?. *Journal of Antimicrobial Chemotherapy* 2006;**58**(4):822–9.

CF Foundation 1994

Cystic Fibrosis Foundation. Microbiology and Infectious disease in cystic fibrosis. Consensus Conference, Bethesda 1994; Vol. V (Section 1):1–26.

CF Foundation 2001

Cystic Fibrosis Foundation. National Patient Registry. Annual Data Report 2000 [Bethesda, Maryland] 2001.

CF Trust 2009
UK Cystic Fibrosis Trust Antibiotic Group. Antibiotic treatment for Cystic Fibrosis. Report of the UK Cystic Fibrosis Trust Antibiotic Group. 3rd 2009.

Cheng 1996
Cheng K, Smyth RL, Govan JR, Doherty C, Winstanley C, Denning N, et al. Spread of beta-lactam-resistant Pseudomonas aeruginosa in a cystic fibrosis clinic. *Lancet* 1996;**348**(9041):1596–7.

Demko 1995
Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: Pseudomonas aeruginosa infection. *Journal of Clinical Epidemiology* 1995;**48**(8):1041–9.

Dodge 2007
Dodge JA, Lewis PA, Stanton M, Wilsher J. Cystic fibrosis mortality and survival in the UK: 1947-2003. *European Respiratory Journal* 2007;**29**(3):522–6.

Donaldson 2003
Donaldson SH, Boucher RC. Update on pathogenesis of cystic fibrosis lung disease. *Current Opinion in Pulmonary Medicine* 2003;**9**(6):486–91.

Doring 2000
Doring G, Conway SP, Heijerman HGM, Hodson ME, Hoiby N, Smyth A, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. *European Respiratory Journal* 2000;**16**(4): 749–67.

Döring 2012
Döring G, Flume P, Heijerman H, Elborn JS, Consensus Study Group. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *Journal of Cystic Fibrosis* 2012;**11**(6):461–79.

Edenborough 2004
Edenborough FP, Stone HR, Kelly SJ, Zadik P, Doherty CJ, Govan JR. Genotyping of Pseudomonas aeruginosa in cystic fibrosis suggests need for segregation. *Journal of Cystic Fibrosis* 2004;**3**(1):37–44.

Elborn 2004
Elborn JS. Difficult bacteria, antibiotic resistance and transmissibility in cystic fibrosis. *Thorax* 2004;**59**(11): 914–5.

Elbourne 2002
Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Emerson 2002
Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson R L. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatric Pulmonology* 2002;**34**(2):91–100.

Frangolias 1999
Frangolias DD, Mahenthiralingam E, Rae S, Raboud JM, Davidson AG, Wittmann R, et al. Burkholderia cepacia in cystic fibrosis: variable disease course. *American Journal of Respiratory and Critical Care Medicine* 1999;**160**(5 Pt 1): 1572–7.

Gibson 2003
Gibson RL, Burns JL, Ramsey RL. Pathophysiology and management of pulmonary infections in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2003;**168**(8):918–51.

Gilligan 1999
Gilligan PH. Microbiology of CF Lung Disease. In: Yankaskas JR, Knowles MR editor(s). *Cystic Fibrosis in Adults*. Philedelpia: Lippincott-Raven, 1999:93–114.

Gold 1987
Gold R, Carpenter S, Heurter H, Corey M, Levison H. Randomized trial of ceftazidime versus placebo in the management of acute respiratory exacerbations in patients with cystic fibrosis. *Journal of Pediatrics* December 1987; **111**:907–13.

Hansen 2008
Hansen CR, Pressler T, Høiby N. Early aggressive eradication therapy for intermittent Pseudomonas Aeruginosa airway colonisation in cystic fibrosis patients: 15 years experience. *Journal of Cystic Fibrosis* 2008;**7**(6): 523–530.

Hentzer 2001
Hentzer M, Teitzel GM, Balzer GJ, Heydorn A, Molin S, Givskov M, et al. Alginate overproduction affects Pseudomonas aeruginosa biofilm structure and function. *Journal of Bacteriology* 2001;**183**(18):5395–401.

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org.

Hodson 2000a
Hodson ME, Geddes DM. *Cystic Fibrosis*. 2nd Edition. Boston: Arnold, 2000.

Hodson 2000b
Hodson ME. Treatment of cystic fibrosis in the adult. *Respiration* 2000;**67**(6):595–607.

Hoogkamp 1983
Hoogkamp-Korstanje JA, van der Laag J. Piperacillin and tobramycin in the treatment of Pseudomonas lung infections in cystic fibrosis. *Journal Antimicrobial Chemotherapy* 1983; **12**(2):175–83.

Horre 2004
Horre R, Schaal KP, Siekmeier R, Sterzik B, de Hoog GS, Schnitzler N. Isolation of fungi, especially Exophiala

dermatitidis, in patients suffering from cystic fibrosis. A prospective study. *Respiration* 2004;**71**(4):360–6.

Hyatt 1981
Hyatt AC, Chipps BE, Kumor KM, Mellits ED, Lietman PS, Rosenstein BJ. A double-blind controlled trial of anti-Pseudomonas chemotherapy of acute respiratory exacerbations in patients with cystic fibrosis. *Journal of Pediatrics* 1981;**99**(2):307–14.

Høiby 2000
Høiby N. Prospects for the prevention and control of pseudomonal infection in children with cystic fibrosis. *Paediatric Drugs* 2000;**2**(6):451–63.

Jones 2001
Jones AM, Govan JR, Doherty CJ, Dodd ME, Isalska BJ, Stanbridge TN, et al. Spread of a multiresistant strain of Pseudomonas aeruginosa in an adult cystic fibrosis clinic. *Lancet* 2001;**358**(9281):557–8.

Jones 2002
Jones AM, Dodd ME, Doherty CJ, Govan JR, Webb AK. Increased treatment requirements of patients with cystic fibrosis who harbour a highly transmissible strain of Pseudomonas aeruginosa. *Thorax* 2002;**57**(11):924–5.

Koch 1991
Koch C, Hjelt K, Pedersen SS, Jensen ET, Jensen T, Lanng S, et al. Retrospective clinical study of hypersensitivity reactions to astreonam and six other beta-lactam antibiotics in cystic fibrosis patients receiving multiple antibiotic courses. *Reviews of Infectious Diseases* 1991;**13**(Suppl 7): S608–11.

Kosorok 1996
Kosorok MR, Wei WH, Farrell PM. The incidence of cystic fibrosis. *Statistics in Medicine* 1996;**15**(5):449–62.

Lechtzin 2006
Lechtzin N, John M, Irizarry R, Merlo C, Diette GB, Boyle MP. Outcomes of adults with cystic fibrosis infected with antibiotic-resistant Pseudomonas aeruginosa. *Respiration* 2006;**73**(1):27–33.

Master 2001
Master V, Roberts GW, Coulthard KP, Baghurst PA, Martin A, Roberts ME, et al. Efficacy of once-daily tobramycin monotherapy for acute pulmonary exacerbations of cystic fibrosis: a preliminary study. *Pediatric Pulmonology* 2001; **31**(5):367–76.

McLaughlin 1983
McLaughlin FJ, Matthew WJ, Strieder DJ, Goldman DA. Clinical and bacteriological responses to three antibiotic regimens for acute exacerbation of cystic fibrosis: Ticarcillin-tobramycin, azlocillin-tobramycin, and azlocillin-placebo. *Journal of Infectious Diseases* 1983;**147**(3):559–67.

Mendelman 1985
Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. *American Review of Respiratory Disease* 1985;**132**(4):761–5.

Olesen 2006
Olesen HV, Nielsen LP, Schiotz PO. Viral and atypical bacterial infections in the outpatient pediatric cystic fibrosis clinic. *Pediatric Pulmonology* 2006;**41**(12):1197–204.

Parmar 2005
Parmar JS, Nasser S. Antibiotic allergy in cystic fibrosis. *Thorax* 2005;**60**(6):517–20.

Penketh 1983
Penketh AR, Hodson ME, Batten JC. Ticarcillin compared with carbenicillin in the treatment of exacerbations of bronchopulmonary infection in cystic fibrosis. *British journal of diseases of the chest* 1983;**77**(2):179–84.

Penketh 1984
Penketh A, Hodson ME, Gaya H, Batten JC. Azlocillin compared with carbenicillin in the treatment of bronchopulmonary infection due to Pseudomonas aeruginosa in cystic fibrosis. *Thorax* 1984;**39**(4):299–304.

Penketh 1987
Penketh AR, Wise A, Mearns MB, Hodson ME, Batten JC. Cystic fibrosis in adolescents and adults. *Thorax* 1987;**42** (7):526–32.

Petersen 1981
Petersen NT, Hoiby N, Mordhorst CH, Lind K, Flensborg EW, Bruun B. Respiratory infections in cystic fibrosis patients caused by virus, chlamydia and mycoplasma - possible synergism with Pseudomonas aeruginosa. *Acta Paediatrica Scandinavica* 1981;**70**(5):623–8.

Rabin 2004
Rabin HR, Butler SM, Wohl MEB, Geller DE, Colin AA, Schidlow DV, et al. Pulmonary exacerbation in cystic fibrosis. *Pediatric Pulmonology* 2004;**37**(5):400–6.

Ramsey 1996
Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. *New England Journal of Medicine* 1996; **335**(3):179–88.

Rosenberg 1993
Rosenberg SM, Schramm CM. Predictive value of pulmonary function testing during pulmonary exacerbations in cystic fibrosis. *Pediatric Pulmonology* 1993;**16**(4):227–35.

Schaedel 2002
Schaedel C, de Monestrol I, Hjelte L, Johannesson M, Kornfalt R, Lindblad A, et al. Predictors of deterioration of lung function in cystic fibrosis. *Pediatric Pulmonology* 2002; **33**(6):483–91.

Smyth 2005
Smyth A, Tan KH, Hyman-Taylor P, Mulheran M, Lewis S, Stableforth D, et al. Once versus three-times daily regimens of tobramycin treatment for pulmonary exacerbations of cystic fibrosis--the TOPIC study: a randomised controlled trial. *Lancet* 2005;**365**(9459):573–8.

Starner 2005
Starner TD, McCray PB Jr, American College of Physicians, American Physiological Society. Pathogenesis of early lung disease in cystic fibrosis: A window of opportunity to

eradicate bacteria. *Annals of Internal Medicine* 2005;**143** (11):816–22.

Stuart 2010

Stuart B, Lin JH, Mogayzel Jr PJ. Early eradication of Pseudomonas Aeruginosa in Patients with Cystic Fibrosis. Review Article. *Peadiatric Respiratory Reviews* 2010;**11**(3): 117–184.

Vic 1998

Vic P, Ategbo S, Turck D, Husson MO, Launay V, Loeuille GA, et al. Efficacy, tolerance, and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. *Archives of Disease in Childhood* 1998;**78**(6):533–9.

Wat 2003

Wat D. Impact of respiratory viral infections on cystic fibrosis. *Postgraduate Medical Journal* 2003;**79**(930):201–3.

References to other published versions of this review

Plummer 2011

Plummer A, Wildman M. Duration of intravenous antibiotic therapy in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD006682.pub3]

Plummer 2013

Plummer A, Wildman M. Duration of intravenous antibiotic therapy in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: 10.1002/14651858.CD006682.pub4]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Adeboyeku 2011	Not duration of treatment, comparison of 2x vs 3x daily antibiotics for pulmonary exacerbations
Blumer 2005	Not duration of treatment, compared different courses of antibiotics
Hjelte 1988	Not duration of treatment, effect of home intravenous antibiotics on quality of life
Hubert 2009	Pharmacokinetic study.
Kapranov 1995	Not intravenous antibiotics or duration of treatment.
Keel 2011	Comparison of oral versus intravenous 2x daily linezolid for nine doses in each group
Kenny 2009	Eradication therapy - an exclusion criteria.
Knight 1979	Not intravenous antibiotics or duration of treatment.
Latzin 2008	Length of therapy varies and not specified.
Postnikov 2007	Twice versus daily dosing not duration of treatment.
Riethmueller 2009	Not duration of treatment, study of elective 3x daily antibiotics for chronic *Pseudomonas aeruginosa*.
Semykin 2010	Not duration of treatment, comparison of different courses of antibiotics for pulmonary exacerbations where all patients got 14 days of antibiotics

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 20 July 2016.

Date	Event	Description
20 July 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group did not identify any new studies potentially eligible for inclusion in the review. Five additional references to two already excluded studies were identified (Hubert 2009; Riethmueller 2009).
20 July 2016	New citation required but conclusions have not changed	A new author, Tim Gleeson, has joined the review team at this review update and is now lead author No new data have been added to the review, therefore our conclusions remain the same

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2008

Date	Event	Description
27 March 2013	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Review Group's Cystic Fibrosis Register identified five new references to four studies potentially eligible for inclusion in this review; all were excluded (Adeboyeku 2011; Keel 2011; Riethmueller 2009; Semykin 2010).
27 March 2013	New citation required but conclusions have not changed	No new studies were included in this update of the review, therefore our conclusions have not changed
3 December 2010	New search has been performed	A search of the Group's Cystic Fibrosis Register identified six new references. The references were all excluded from this review, as was the one outstanding reference awaiting classification from the original review (Hjelte 1988).
3 December 2010	New citation required but conclusions have not changed	The lead author (Martin Wildman) has stepped down from this role, but remains a co-author on this review.

(*Continued*)

		The lead author is now Amanda Plummer. One author (Bryan Fernandes) has left the author team
1 April 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any references eligible for inclusion in this review
31 March 2008	Amended	Converted to new review format. Post hoc change: see Long-term outcomes two primary outcome measures have been more appropriately re-classified as secondary outcome measures

CONTRIBUTIONS OF AUTHORS

Original protocol and review	
Task	**Author**
Conceiving the review	MW, BF
Designing the review	MW, BF, AP
Coordinating the review	MW
Data collection for the review	BF, AP
Developing search strategy	MW, BF, AP
Undertaking searches	BF, AP
Screening search results	BF, AP
Organising retrieval of papers	BF, AP
Screening retrieved papers against inclusion criteria	BF, AP
Appraising quality of papers	BF, AP
Abstracting data from papers	BF, AP
Writing to authors of papers for additional information	BF, AP
Providing additional data about papers	MW, BF, AP

(*Continued*)

Obtaining and screening data on unpublished studies	BF, AP
Data management for the review	BF, AP
Entering data into RevMan	BF, AP
Analysis of data	BF, AP
Interpretation of data	MW, BF, AP
Providing a methodological perspective	MW, BF, AP
Providing a clinical perspective	MW, BF, AP
Providing a policy perspective	MW
Writing the review	MW, BF, AP
Providing general advice on the review	MW

Updates of review	
Task	**Author**
Screening search results	AP, MW,TG
Organising retrieval of papers	AP,TG
Screening retrieved papers against inclusion criteria and appraising risk of bias	AP, MW,TG
Abstracting data from papers	AP, MW
Writing to authors of papers for additional information	AP
Data management for the updated review and data entry	AP
Analysis and interpretation of data	AP, MW
Providing a methodological and clinical perspective	AP, MW
Providing a policy perspective	MW
Writing the update	AP, MW,TG

(*Continued*)

Providing general advice on the review	AP,MW

DECLARATIONS OF INTEREST

Tim Gleeson declares he has received support from Actavis in the form of travel and accomodation to enable him to attend the CF Pharmacists study day and steering committee meeting.

Martin Wildman works intensively in the area of adherence working to understand how preventative nebulised treatment can decrease the need for IV antibiotics. He has received support from Respironics in terms of salary support for a research fellow who has worked on adherence research. He has also received funding from Smiths Medical for work around adherence device developments, funding from Pari to develop software to measure drug duration, and funding from Philips to use airflow data to try to predict exacerbations.

Amanda Plummer declares no known potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

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NOTES

At the update in 2010 Dr Bryan Fernandes left the review team and Amanda Plummer took on the role of lead author.

At the update in 2015 Tim Gleeson joined the review team for the review update.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Bacterial Infections [*drug therapy]; Cystic Fibrosis [*complications]; Drug Administration Schedule; Injections, Intravenous; Lung Diseases [*drug therapy]

MeSH check words

Humans