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

Abbott L, Plummer A, Hoo ZH, Wildman M

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[Intervention Review]

Duration of intravenous antibiotic therapy in people with cystic fibrosis

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ABSTRACT

Background

Progressive lung damage from recurrent exacerbations 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. The risk of systemic side effects such as allergic reactions to antibiotics also increases with prolonged courses and the use of aminoglycosides requires frequent monitoring to minimise 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: 30 May 2019.

We also searched online trials registries. Most recent search of the ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) portal: 06 January 2019.

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 for inclusion. A trial looking at the standardised treatment of pulmonary exacerbations is currently ongoing and will be included when the results are published.

Main results

No eligible trials were included.

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 adherence, result in a reduced incidence of drug reactions and be less costly. However, the shorter duration 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. The currently ongoing STOP2 trial is expected to provide some guidance on these questions when published.

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: 30 May 2019.

Study characteristics

No completed studies have compared different lengths of treatment with intravenous antibiotics, but there is one study under way looking at this question. When the results are published, we plan to include the study in this review.

Key results

Further research is needed to find the best duration of treatment for exacerbations. 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.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common life-limiting autosomal recessive genetic disorder in people of northern European descent

(Farrell 2018), affecting over 10,000 individuals in the UK (Keogh 2018). 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 with over half of people born today predicted to live at least 47 years (Keogh 2018). One of the major reasons for this increase in survival is the increased 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* and *Haemophilus influenzae* are the most common organisms isolated and thought to be responsible for chest exacerbations. In older children and adults, the major pathogen is *Pseudomonas aeruginosa. Burkholderia cepacia* and *non-tuberculous mycobacteria* are also of concern (UK CF Trust 2018). 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 2000). 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 25.7% in 16 to 19 year olds, rising to a peak of 55.7% in 36 to 39 year olds and a median in adults of 44.5% (UK CF Trust 2018). 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 forced expiratory volume in one second (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* 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 influenced by recent culture results of airway secretions, individual tolerance and previous clinical results. In infections caused by *P aeruginosa*, a combination of an aminoglycoside and a 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. Yet the cause of treatment failure is complex and varied (Parkins 2012). 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 2000). The optimal duration of intravenous antibiotic therapy is not clearly defined (Flume 2009). There is a school of thought that there is limited evidence for fixed durations of treatment and instead to treat until symptoms are improved and the individual is close to baseline (Stephen 2018). 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; Döring 2012; 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). Some studies also mention 10 days (CF Trust 2009; Doring 2000; Hodson 2000) 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 2000).

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; Plummer 2016).

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-RCTs.

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 11 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 oxygen 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

There were no restrictions due to language or publication status.

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 website. Date of most recent search of the Cystic Fibrosis Trials Register: 30 May 2019.

We also searched the online trials databases as detailed in the appendices (Appendix 1). Date of latest search: 06 January 2019.

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, LA or ZHH) 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, LA or ZHH) 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 (adverse effects, treatment failure), 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 (lung function, change in sputum bacteriology, quality of life, change in nutritional status, change in inflammatory markers), we plan to record either mean relative change from baseline for each group or mean post-treatment or intervention values and standard deviation (SD). If standard errors (SEs) are reported, and where possible, these will be converted to SDs. We will calculate a pooled estimate of treatment effect by calculating the mean difference (MD) with corresponding 95% confidence intervals (CIs).
For any time-to-event outcome included in the review (time to next exacerbation), 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 SEs 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 we detect asymmetry, we will explore causes other than publication bias.

Data synthesis

If we do not identify substantial heterogeneity (as defined above), 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 substantial 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 HIVAT 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 16 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.

Summary of findings tables

In a post hoc change, we plan to present a summary of findings table for each comparison we report in the review. In each table we will present the results of the following outcomes:

1. absolute change in % predicted FEV_1 pre and post IV antibiotic course;
2. absolute change in % predicted FVC pre and post antibiotic course;
3. time to next exacerbation;
4. adverse events.

We will determine the quality of the evidence using the GRADE approach; and will downgrade evidence in the presence of a high risk of bias in at least one study, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results or high probability of publication bias. We will downgrade evidence by one level for a serious limitation and by two levels if very serious.

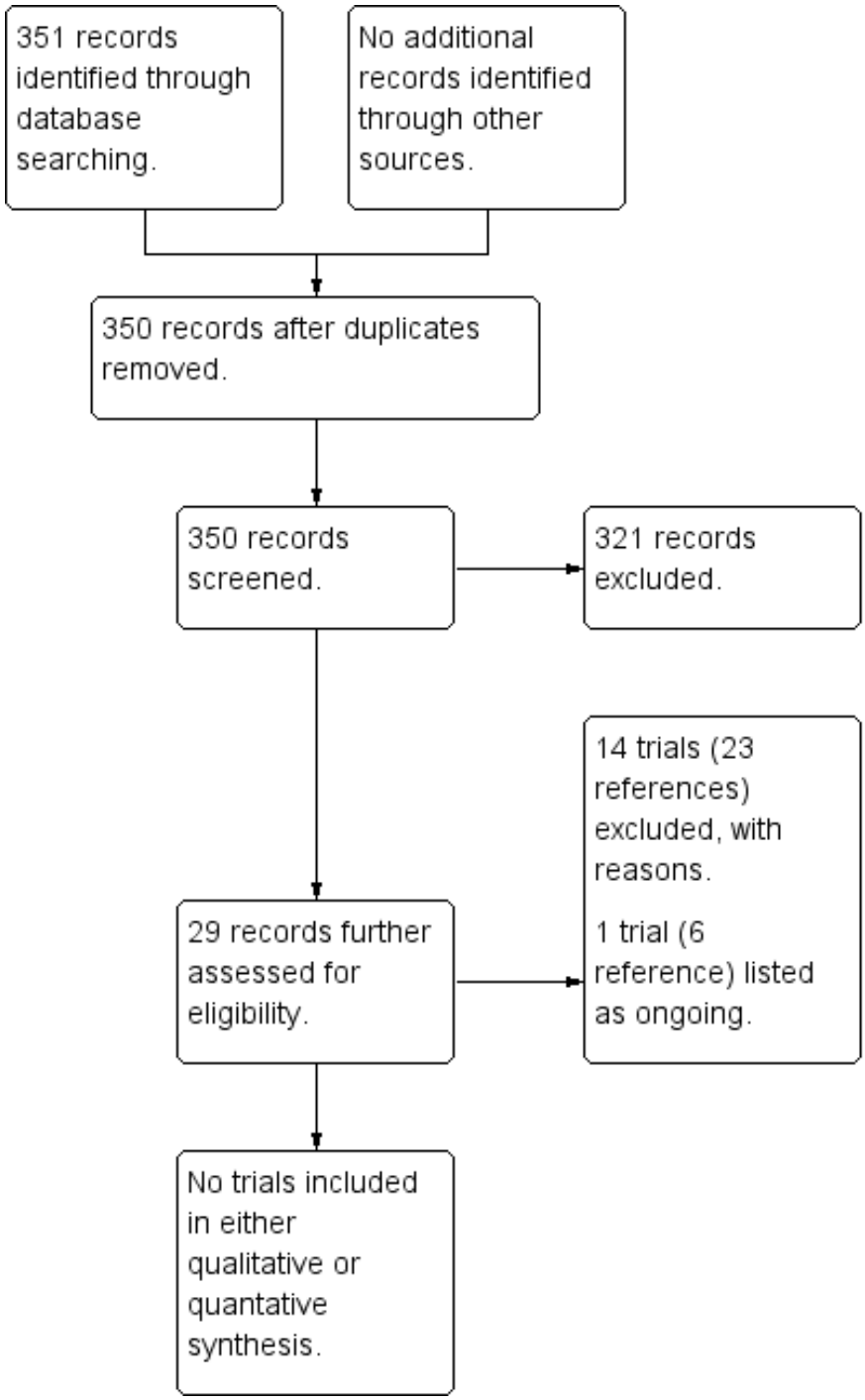
RESULTS

Description of studies

Results of the search

A total of 297 papers were obtained from the Group's Cystic Fibrosis Trials Register and a further 54 records from online trials registries - as detailed in the PRISMA diagram (Figure 1). Out of the papers identified from the Group's Cystic Fibrosis Trials Register, only 84 papers involved treatment of chest exacerbations with intravenous antibiotics. The rest of the trials were excluded immediately because they involved oral or nebulised antibiotics or were pharmacokinetic trials, trials concerning method of delivery or without any clinical outcome measures. None of the RCTs identified compared different durations of antibiotic courses and are therefore not eligible for inclusion in this review. We have excluded 14 trials (23 references) and the reasons for exclusion are provided in the tables (Characteristics of excluded studies). We have identified one ongoing trial (six references) (STOP2).

Figure 1. Study flow diagram.



Included studies

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

Excluded studies

A total of 14 trials were excluded. One trial was abandoned due to low recruitment (NCT01044719), another was excluded due to its observational trial design (STOP 2017) and the remaining 12 trials did not compare duration of treatment with IV antibiotics (Adeboyeku 2011; Blumer 2005; Hjelte 1988; Hubert 2009; Kapranov 1995; Keel 2011; Kenny 2009; Knight 1979; Latzin 2008; Postnikov 2007; Riethmueller 2009; Semykin 2010).

Ongoing studies

One trial is listed as ongoing and expected to report results in 2020 (STOP2). This RCT has a parallel design with three separate arms. It is a multicentre trial being run at 58 centres in the USA and Canada (only one of the centres is in Canada). Participants are adults (18 years and over) and of either gender, who are being treated with IV antibiotics for a pulmonary exacerbation; they can only participate once in this trial. Courses of antibiotics of different durations are being compared (10 days versus 14 days versus 21 days) and may be administered either in hospital or at home. The treating physician will decide on the choice of antibiotics. The primary outcome is the change from baseline in FEV_1 % predicted at 14 days after the course of antibiotics has been completed. Secondary outcomes are a change in symptom score and a change in weight at the same time point (STOP2).

Risk of bias in included studies

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

Effects of interventions

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

DISCUSSION

CF is a life-limiting disease. While every effort needs to be focused on treating chest infections aggressively, there is still no clear guidance on how long the optimum duration of IV antibiotics should be. 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.

One prospective observational study identified the mean duration of IV antibiotics as 15.9 days but this varied according to an individual's characteristics (STOP 2017). A USA registry analysis determined that treatment courses less than nine days are associated with early treatment failure and 10 days is considered to be the minimum duration (VanDevanter 2016). A further study has suggested that there may be benefit with extending IV duration beyond 14 days for some people (Waters 2015). 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 Cochrane 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.

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 the duration of antibiotic therapy would not be expected to result in the 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.

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). UK prevalence data indicates a rate of infection with *Mycobacterium abcessus* of 3.8% (UK CF Trust 2018) and significantly longer durations of IV antibiotics may be required to treat this organism. Current recommendations in the UK advise a minimum of one month of IV antibiotics for initial treatment, with the duration determined by severity of infection, response to treatment and tolerability of the regimen (BTS 2017).

AUTHORS' CONCLUSIONS

Implications for practice

There are no published data to recommend the optimum duration

of intravenous antibiotic therapy for treating a chest exacerbation in people with cystic fibrosis. 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. The role of nebulised antibiotics to replace IV antibiotics may have implications for practice but is outside the remit of this review.

Implications for research

This Cochrane Review has identified the need for a well-designed, adequately-powered, multicentre randomised controlled trial to assess the optimum duration of intravenous antibiotic therapy to treat chest exacerbations in people with cystic fibrosis, an issue which has important clinical and financial implications. This question is expected to be addressed by the identified ongoing trial which is due for completion in 2020 (STOP2).

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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 2011	Not duration of treatment, comparison of 2x versus 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 9 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.
NCT01044719	Abandoned due to low recruitment.
Postnikov 2007	2x versus 1x 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 participants received 14 days of antibiotics
STOP 2017	Observational study.

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

STOP2

Trial name or title	Standardized Treatment of Pulmonary Exacerbations II (STOP2)
Methods	RCT. Design: parallel with 3-arms. Location: USA and Canada. Multicentre: 58 centres.

STOP2 (*Continued*)

Participants	Target recruitment is 1300 participants. **Inclusion criteria** • Male or female ≥18 years of age at Visit 1 • Documentation of a CF diagnosis • Enrolled in the CF Foundation National Patient Registry prior to Visit 1 (USA sites only) • At the time of Visit 1, there is a plan to initiate IV antibiotics for a pulmonary exacerbation • Performed spirometry at Visit 1 and Visit 2 and willing to perform spirometry at Visit 3 • Completed the CRISS questionnaire at Visit 1 and Visit 2 and willing to complete the Cystic Fibrosis Respiratory Symptoms Diary (CFRSD) questionnaire at Visit 3 • Willing to adhere to a specific treatment duration determined by initial response to treatment and subsequent randomization • Willing to return for follow up Visit 3 • Written informed consent obtained from the participant or their legal representative **Exclusion criteria** • Previous randomization in this study • Treatment with IV antibiotics in the 6 weeks prior to Visit 1 • Admission to the intensive care unit for current pulmonary exacerbation in the 2 weeks prior to Visit 2, unless admission was due to a desensitization protocol • Pneumothorax in the 2 weeks prior to Visit 2 • Primary diagnosis for current hospitalization is unrelated to worsening lower respiratory symptoms (e.g., pulmonary clean out, DIOS, sinusitis) • Massive haemoptysis defined as > 250 cc in a 24 hour period or 100 cc/day over 4 consecutive days occurring in the 2 weeks prior to Visit 2 • Current pulmonary exacerbation thought to be due to ABPA • At Visit 1, receiving ongoing treatment with a duration of more than 2 weeks with prednisone equivalent to >10 mg/day • History of solid organ transplantation • Receiving antimicrobial therapy to treat non-tuberculous mycobacterium (e.g., *M abscessus*, *M avium complex*) in the 2 weeks prior to Visit 2
Interventions	**Arm 1**: IV antibiotics (to be selected by treating physician) for 10 days **Arm 2**: IV antibiotics (to be selected by treating physician) for 14 days **Arm 3**: IV antibiotics (to be selected by treating physician) for 21 days *Note*: differing durations of IV treatment to be given in the hospital or at home for a pulmonary exacerbation
Outcomes	Primary outcome: absolute FEV_1 % predicted - change from baseline to 14 days post IV completion Secondary outcomes: change in CRISS score from baseline to 14 days post IV completion; change in weight from baseline to 14 days post IV completion
Starting date	June 2016 (estimated completion date - February 2020)
Contact information	Principle investigators: Chris Goss and Patrick Flume. Chris Goss, MD University of Washington Medical Center, 1959 N.E. Pacific, Campus Box 356522, Seattle, WA 98195-6522, USA Telephone: +1 206 616 1058 Email: goss@u.washington.edu Patrick Flume, MD

STOP2 (*Continued*)

	Department of Medicine, Division of Pulmonary and Critical Care, Medical University of South Carolina, 96 Jonathan Lucas Street, 812-CSB, Charleston South Carolina 29403, USA Telephone: +1 843 792 9219 Email: flumepa@musc.edu
Notes	Clinical trial identifier: NCT02781610 Collaborators: Cystic Fibrosis Foundation; CF Therapeutics Development Network Coordinating Center; Medical University of South Carolina; University of Washington

ABPA: allergic bronchopulmonary aspergillosis
CF: cystic fibrosis
CFRSD: cystic fibrosis respiratory symptoms diary
CRISS: chronic respiratory infection symptom score
DIOS: distal intestinal obstruction syndrome
FEV_1: forced expiratory volume in 1 second
IV: intravenous

APPENDICES

Appendix 1. Search strategies for online databases

Database	Search terms	Date last searched
ClinicalTrials.gov (clinicaltrials.gov/)	Status: all studies Condition/Disease: cystic fibrosis Other terms: intravenous antibiotic	06 January 2019
WHO ICTRP portal (apps.who.int/trialsearch/)	Search term: cystic AND fibrosis AND intravenous AND antibiotic Phases: all	06 January 2019

WHAT'S NEW

Date	Event	Description
22 August 2019	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group and additional searches identified nine new references potentially eligible for inclusion in the review One new reference to an already excluded trial was identified (Hubert 2009). We identified two new trials: one (with two references) was excluded (abandoned due to low recruitment) (NCT01044719); and one trial (with six references) is listed as ongoing with results expected in 2020 (STOP2) .
22 August 2019	New citation required but conclusions have not changed	Two new authors have joined the review team (Linsey Abbott and Zhe Hui Hoo) and one author has stepped down (Tim Gleeson) The some text sections of the review have been updated to ensure continued relevance and to reflect current opinion and practice

HISTORY

Protocol first published: Issue 3, 2007

Review first published: Issue 2, 2008

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
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).

(*Continued*)

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 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. The lead author is now Amanda Plummer. One author (Bryan Fernandes) has left the author team
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).
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, AP
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

(*Continued*)

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
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, LA, ZHH
Organising retrieval of papers	AP,TG, LA, ZHH
Screening retrieved papers against inclusion criteria and appraising risk of bias	AP, MW,TG, LA, ZHH
Abstracting data from papers	AP, MW, LA, ZHH
Writing to authors of papers for additional information	AP, ZHH

(*Continued*)

Data management for the updated review and data entry	AP, LA, ZHH
Analysis and interpretation of data	AP, MW, LA, ZHH
Providing a methodological and clinical perspective	AP, MW, LA, ZHH
Providing a policy perspective	MW
Writing the update	AP, MW,TG, LA, ZHH
Providing general advice on the review	AP,MW

DECLARATIONS OF INTEREST

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. He has also been paid for consultancy relating to adherence by Vertex Inc (Vertex do not manufacture or market antibiotics).

Amanda Plummer has received an honrarium from Profile Pharmaceuticals and from the Chiesi advisory board related to preventative nebulised treatment; these do not constitute a conflict of interest for this review which is looking at the duration of intravenous antibiotic treatment.

Linsey Abbott declares no known potential conflict of interest.

Zhe Hui Hoo declares funding from a CF Trust clinical fellowship (Award Identifier CF007).

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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.

At the update in 2019 Linsey Abbott and Dr Zhe Hui Hoo joined the team, replacing Tim Gleeson.

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