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[Intervention Review]

Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis

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ABSTRACT

Background

Respiratory tract infection with *Pseudomonas aeruginosa* occurs in most people with cystic fibrosis. Once chronic infection is established, *Pseudomonas aeruginosa* is virtually impossible to eradicate and is associated with increased mortality and morbidity. Early infection may be easier to eradicate.

This is an update of a Cochrane review first published in 2003, and previously updated in 2006, 2009 and 2014.

Objectives

To determine whether antibiotic treatment of early *Pseudomonas aeruginosa* infection in children and adults with cystic fibrosis eradicates the organism, delays the onset of chronic infection, and results in clinical improvement. To evaluate whether there is evidence that a particular antibiotic strategy is superior to or more cost-effective than other strategies and to compare the adverse effects of different antibiotic strategies (including respiratory infection with other micro-organisms).

Search methods

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

Most recent search: 10 October 2016.

Selection criteria

We included randomised controlled trials of people with cystic fibrosis, in whom *Pseudomonas aeruginosa* had recently been isolated from respiratory secretions. We compared combinations of inhaled, oral or intravenous antibiotics with placebo, usual treatment or other combinations of inhaled, oral or intravenous antibiotics. We excluded non-randomised trials, cross-over trials, and those utilising historical controls.

Data collection and analysis

Both authors independently selected trials, assessed risk of bias and extracted data.

Main results

The search identified 60 trials; seven trials (744 participants) with a duration between 28 days and 27 months were eligible for inclusion. Three of the trials are over 10 years old and their results may be less applicable today given the changes in standard treatment. Some of the trials had low numbers of participants and most had relatively short follow-up periods; however, there was generally a low risk of bias from missing data. In most trials it was difficult to blind participants and clinicians to treatment given the interventions and comparators used. Two trials were supported by the manufacturers of the antibiotic used.

Evidence from two trials (38 participants) at the two-month time-point showed treatment of early *Pseudomonas aeruginosa* infection with inhaled tobramycin results in microbiological eradication of the organism from respiratory secretions more often than placebo, odds ratio 0.15 (95% confidence interval (CI) 0.03 to 0.65) and data from one of these trials, with longer follow up, suggested that this effect may persist for up to 12 months.

One randomised controlled trial (26 participants) compared oral ciprofloxacin and nebulised colistin versus usual treatment. Results after two years suggested treatment of early infection results in microbiological eradication of *Pseudomonas aeruginosa* more often than no anti-pseudomonal treatment, odds ratio 0.12 (95% CI 0.02 to 0.79).

One trial comparing 28 days to 56 days treatment with nebulised tobramycin solution for inhalation in 88 participants showed that both treatments were effective and well-tolerated, with no notable additional improvement with longer over shorter duration of therapy. However, this trial was not powered to detect non-inferiority or equivalence .

A trial of oral ciprofloxacin with inhaled colistin versus nebulised tobramycin solution for inhalation alone (223 participants) failed to show a difference between the two strategies, although it was underpowered to show this. A further trial of inhaled colistin with oral ciprofloxacin versus nebulised tobramycin solution for inhalation with oral ciprofloxacin also showed no superiority of the former, with increased isolation of *Stenotrophomonas maltophilia* in both groups.

A recent, large trial in 306 children aged between one and 12 years compared cycled nebulised tobramycin solution for inhalation to culture-based therapy and also ciprofloxacin to placebo. The primary analysis showed no difference in time to pulmonary exacerbation or proportion of *Pseudomonas aeruginosa* positive cultures. An analysis performed in this review (not adjusted for age) showed fewer participants in the cycled therapy group with one or more isolates of *Pseudomonas aeruginosa,* odds ratio 0.51 (95% CI 0.31 to 0.28).

Using GRADE, the quality of evidence for outcomes was downgraded to moderate to very low. Downgrading decisions for *Pseudomonas aeruginosa* eradication and lung function were based on applicability (participants mostly children) and limitations in study design, with imprecision an additional limitation for lung function, growth parameters and adverse effects.

Authors' conclusions

We found that nebulised antibiotics, alone or in combination with oral antibiotics, were better than no treatment for early infection with *Pseudomonas aeruginosa*. Eradication may be sustained for up to two years. There is insufficient evidence to determine whether antibiotic strategies for the eradication of early *Pseudomonas aeruginosa* decrease mortality or morbidity, improve quality of life, or are associated with adverse effects compared to placebo or standard treatment. Four trials comparing two active treatments have failed to show differences in rates of eradication of *Pseudomonas aeruginosa.* There have been no published randomised controlled trials that investigate the efficacy of intravenous antibiotics to eradicate *Pseudomonas aeruginosa* in cystic fibrosis. Overall, there is still insufficient evidence from this review to state which antibiotic strategy should be used for the eradication of early *Pseudomonas aeruginosa* infection in cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Different ways of giving antibiotics to eradicate *Pseudomonas aeruginosa* infection in people with cystic fibrosis

Review question

What is the best way of using antibiotics to eliminate lung infections caused by a germ called *Pseudomonas aeruginosa* in people with cystic fibrosis?

Background

Cystic fibrosis is an inherited condition where the airways often become blocked with mucus. It is associated with chest infections, which can lead to progressive breathing failure and death. A germ called *Pseudomonas aeruginosa* is often the cause of infection and is difficult to treat successfully, once infection has become established.

We wanted to compare different combinations of inhaled, oral and intravenous (IV) antibiotics for eliminating *Pseudomonas aeruginosa* in people with cystic fibrosis to see if any single treatment works best and is more cost-effective.

Search date

The evidence is current to 10 October 2016.

Study characteristics

We included seven trials with 744 people with cystic fibrosis of both sexes, any age and both mild and more severe lung disease. The trials lasted from 28 days to 27 months. We could not combine many results as trials used different treatments. Two trials compared tobramycin to placebo (a dummy treatment). Three trials combined oral ciprofloxacin and inhaled colistin in the experimental group but used different comparators - one compared the antibiotic combination to no treatment, one to inhaled tobramycin and the third to oral ciprofloxacin with inhaled tobramycin. Another trial considered inhaled tobramycin and compared 28 days of treatment to 56 days. The final trial compared regular cycles of inhaled tobramycin (plus oral ciprofloxacin or placebo) to only treating with inhaled tobramycin (plus oral ciprofloxacin or placebo) based on the results of cultures grown in the laboratory.

Key results

Two small trials (38 people) treating early infection showed that after two months inhaled antibiotics were better than no treatment and eliminated *Pseudomonas aeruginosa* in most people. One of these trials reported for longer and suggested that this effect may last for up to 12 months. Another small trial (26 people) which lasted two years showed that treating early infection with a combination of inhaled and oral antibiotics was better than no treatment for eliminating *Pseudomonas aeruginosa*. A trial comparing 28 days of nebulised tobramycin solution for inhalation (88 people) to 56 days showed both were equally tolerated and successful at eliminating *Pseudomonas aeruginosa*. Four direct comparisons of oral or inhaled antibiotics (or combinations of both), including one with 223 people, did not find a difference between different antibiotic combinations. A recent trial in 306 children (aged up to 12 years) compared a regular cycle of inhaled tobramycin (with either oral ciprofloxacin or placebo) to treatment only when it was shown that a child was infected with *Pseudomonas aeruginosa* and showed that when children were given a regular cycle of inhaled tobramycin (with either oral ciprofloxacin or placebo) fewer of them grew *Pseudomonas aeruginosa* from their sputum. The trial report made an adjustment for age and did not show any difference in the number of times *Pseudomonas aeruginosa* was grown from samples between the groups, nor was there any difference in the length of time until the children had their next chest infection.

Quality of the evidence

Some trials were conducted up to 20 years ago and the results may not be applicable today. Some trials were small. All the trials had quite a short follow-up period, so we could not show whether treatment made people with cystic fibrosis feel better or live longer. Given the treatments compared in most of the trials, it would have been easy for people to guess which treatment they were receiving, which might have influenced some of the results. Two trials were supported by the pharmaceutical industry. Further research is still needed to see whether eliminating the bacteria completely improves the well-being and quality of life in people with cystic fibrosis and to establish which antibiotic combination provides the best way of eliminating *Pseudomonas aeruginosa*.

Overall the quality of evidence was moderate to very low, meaning that further research is likely to change the estimate of the size of the treatment effect. Future, larger trials (with greater power) may show one treatment is more effective in eradicating *Pseudomonas aeruginosa* than another.