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Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis

Code: CD001021 **Year:** 2022 **Date:** 2011 - updated: 28 JUN 2022 **Author:** Smith S

Study design (if review, criteria of inclusion for studies)

Trials were selected if inhaled antibiotic treatment was used for at least four weeks in people with CF, treatment allocation was randomised or quasi-randomised, and there was a control group (either placebo, no placebo or another inhaled antibiotic).

List of included studies (18)

Assael 2013; Bilton 2014; Chuchalin 2007; Day 1988; Elborn 2015; Flume 2016 b; Hodson 1981; Jensen 1987; Konstan 2010 b; Kun 1984; MacLusky 1989; Murphy 2004; Nathanson 1985; Nikolaizik 2008; Ramsey 1999; Schuster 2013; Stead 1987; Wiesemann 1998

Participants

People with CF diagnosed by clinical features associated with an abnormal sweat electrolyte test or mutations of the CFTR gene or both. All ages and all levels of severity of respiratory disease were included.

Interventions

Inhaled antibiotics (tobramycin); Inhaled anti-pseudomonal antibiotic

Outcome measures

Deaths; Exacerbation of respiratory infection; FEV1 change after single treatment; Frequency of new isolates of drug resistant organisms; Frequency of one or more courses of intravenous antibiotics; Frequency of one or more courses of oral or intravenous antibiotics; Frequency of one or more hospital admissions; Frequency of tobramycin resistant P. aeruginosa at end of study; Hospital admissions, mean number of days in hospital; Mean FEV1 at end of treatment (% predicted); Mean FVC at end of treatment (% predicted); Mean per cent change in FEV1 (% predicted); Mean per cent change in FVC (% predicted); Number experiencing adverse event at end of study; Number experiencing adverse events by end of study; Rate of change of FEV1 (% predicted per year); Rate of change of FVC (% predicted per year); Weight - change (kg)

Main results

The searches identified 410 citations to 125 trials; 18 trials (3042 participants aged between five and 45 years) met the inclusion criteria. Limited data were available for metaâ€•analyses due to the variability of trial design and reporting of results. A total of 11 trials (1130 participants) compared an inhaled antibiotic to placebo or usual treatment for a duration between three and 33 months. Five trials (1255 participants) compared different antibiotics, two trials (585 participants) compared different regimens of tobramycin and one trial (90 participants) compared intermittent tobramycin with continuous tobramycin alternating with aztreonam. One trial (18 participants) compared an antibiotic to placebo and also to a different antibiotic and so fell into both groups. The most commonly studied antibiotic was tobramycin which was studied in 12 trials. Inhaled antibiotics compared to placebo We found that inhaled antibiotics may improve lung function measured in a variety of ways (4 trials, 814 participants). Compared to placebo, inhaled antibiotics may also reduce the frequency of exacerbations (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.47 to 0.93; 3 trials, 946 participants; lowâ€•certainty evidence). Inhaled antibiotics may lead to fewer days off school or work (quality of life measure) (mean difference (MD) â€•5.30 days, 95% CI â€•8.59 to â€•2.01; 1 trial, 245 participants; lowâ€•certainty evidence). There were insufficient data for us to be able to report an effect on nutritional outcomes and there was no effect on survival. There was no effect on antibiotic resistance seen in the two trials that were included in metaâ€•analyses. We are uncertain of the effect of the intervention on adverse events (very lowâ€•certainty evidence), but tinnitus and voice alteration were the only events occurring more often in the inhaled antibiotics group. The overall certainty of evidence was deemed to be low for most outcomes due to risk of bias within the trials and imprecision due to low event rates. Different antibiotics or regimens compared Of the eight trials comparing different inhaled antibiotics or different antibiotic regimens, there was only one trial for each unique comparison. We found no differences between groups for any outcomes except for the following. Aztreonam lysine for inhalation probably improved forced expiratory volume at one second (FEV1) % predicted compared to tobramycin (MD â€•3.40%, 95% CI â€•6.63 to â€•0.17; 1 trial, 273 participants; moderateâ€•certainty evidence). However, the method of defining the endpoint was different to the remaining trials and the participants were exposed to tobramycin for a long period making interpretation of the results problematic. We found no differences in any measure of lung function in the remaining comparisons. Trials measured pulmonary exacerbations in different ways and showed no differences between groups except for aztreonam lysine probably leading to fewer people needing treatment with additional antibiotics than with tobramycin (RR 0.66, 95% CI 0.51 to 0.86; 1 trial, 273 participants;

moderateâ€•certainty evidence); and there were fewer hospitalisations due to respiratory exacerbations with levofloxacin compared to tobramycin (RR 0.62, 95% CI 0.40 to 0.98; 1 trial, 282 participants; highâ€•certainty evidence). Important treatmentâ€•related adverse events were not very common across comparisons, but were reported less often in the tobramycin group compared to both aztreonam lysine and colistimethate. We found the certainty of evidence for these comparisons to be directly related to the risk of bias within the individual trials and varied from low to high.

Authors' conclusions

Longâ€•term treatment with inhaled antiâ€•pseudomonal antibiotics probably improves lung function and reduces exacerbation rates, but pooled estimates of the level of benefit were very limited. The best evidence available is for inhaled tobramycin. More evidence from trials measuring similar outcomes in the same way is needed to determine a better measure of benefit. Longerâ€•term trials are needed to look at the effect of inhaled antibiotics on quality of life, survival and nutritional outcomes.

https://doi.org//10.1002/14651858.CD001021.pub4

See also

Smith S, Rowbotham NJ. Inhaled antiâ€•pseudomonal antibiotics for longâ€•term therapy in cystic fibrosis. Cochrane Database of Systematic Reviews 2022, Issue 11. Art. No.: CD001021. DOI: 10.1002/14651858.CD001021.pub4. Accessed 29 November 2022.

Keywords

Anti-Bacterial Agents; Bacterial Infections; Infection; Inhalation OR nebulised; Intranasal; nebuliser; non pharmacological intervention - devices OR physiotherapy; pharmacological_intervention; Pseudomonas aeruginosa; Pseudomonas; Respiratory Tract Diseases; Respiratory Tract Infections; Amikacin; Aztreonam; Ceftazidime; Ciprofloxacin; Colistin; Fosfomycin; levofloxacin; Tobramycin; Exacerbation; Staphylococcus aureus; Aminoglycosides; Monobactams; Cephalosporins; Quinolones; other anti-bacterial agents;