G.11 Pulmonary infection – chronic

Review question: What is the effectiveness of antimicrobial regimens in suppressing chronic pulmonary infection in children and adults with cystic fibrosis with any of the following pathogens: Pseudomonas Aeruginosa, Burkholderia Cepacia Complex, Staphylococcus Aureus and Aspergillus Fumigatus?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Aaron, S. D., Vandemheen, K. L., Freitag, A., Pedder, L., Cameron, W., Lavoie, A., Paterson, N., Wilcox, P., Rabin, H., Tullis, E., Morrison, N., Ratjen, F., Treatment of Aspergillus	Sample size N=35 (another 32 patients declined to participate)	Interventions Intervention Treatment: itraconazole Formulation: capsules	Details Randomization Central allocation schedule for	Results Lung function - % change in FEV1 predicted	Limitations The Risk of bias was assessed using the Cochrane Risk of Bias tool. Sequence generation: low risk Allocation concealment: unclear risk (the process is not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fumigatus in patients with cystic fibrosis: a randomized, placebo-controlled pilot study, PLoS ONE [Electronic Resource], 7, e36077, 2012 Ref Id 398320 Country/ies where the study was carried out Canada Study type RCT, placebo-controlled Aim of the study To evaluate if treatment directed against A. Fumigatus improves pulmonary function and clinical outcomes in patients with CF. Study dates Jan 2008 - May 2010 Source of funding Not reported	Itraconazole n=18 placebo n=17 Characteristics Age (mean±SD): 25.3±10.5 vs. 25.2±9.1 Male (%): 56% vs 53% FEV1 % predicted (mean±SD): 63.4%±22.2 Coinfections S. Aureous: 39% vs 47% P. Aeruginosa: 39% vs 59% Inclusion criteria 9 Canadian CF clinics	Duration: 24-weeks Dosing: daily dose of 5 mg/kg, as per CF Consensus Guidelines Timing of administration: once daily; if the dose exceeded 200 mg/day it was given twice daily Patients were advised to take the medication with orange juice of cola to maximise oral absorption All patients continued with standard CF medication as prescribed by their physicians Comparison Placebo	randomization through computer generated list, in variable blocks of 2 or 4. Allocation concealment Not reported Blinding Study medication given by site research pharmacist.Research and medical staff were blinded. Data collection Patients underwent study assessments at baseline, 4, 12, 24 and 48 weeks.	from baseline 24-week follow-up period: -4.62% (decline) vs 0.32% (improvement); MD: -4.94% (95% CI: -15.33 to 5.45); adj MD (age, gender, baseline FEV1): -4.85%; p=0.34 48-week follow-up period: MD: -3.71% (95% CI: -13.26 to 20.68) Time to next pulmonary exacerbation Median to 1st exacerbation: 77 vs 134	Blinding: low risk Incomplete data: low risk Selective reporting: unclear risk (the assessments were taken at 4, 12, 24 and 48h and data is only reported for 24 and 48h. Also some results are poorly reported, and cannot be imputed in RevMan) Other: high risk (the sample size is quite small and 32 patients declined to participate) OVERALL QUALITY: moderate risk of bias Other information (+) first prospective RCT (+) ITT analysis (-) pilot study small sample size, authors failed to recruit more patients to extend the study (-) Failure to achieve therapeutic levels of Itraconazole in many patients

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	Confirmed CF diagnoses ≥ 6 years of age Chronically colonised with A, Fumigatus, defined as at least 2 positive sputum cultures within the last 12 months Clinically stable at the time of randomization, with no acute treatment for acute CF pulmonary exacerbation allowed for at least 14 days prior randomization Exclusion criteria Patients were	Same as above	Data analysis Changes in FEV1 were compared using Student t-test. The proportion of patients that experience exacerbations was calculated with Chi-Square. Kaplan Meier survival curves were used to calculate time to first exacerbation.	days; p=0.35 AdjHR (age, gender, baseline FEV1): 1.34 (95% CI: 0.57 to 3.14; p=0.50) proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB 24-week follow-up - 67% (n=12) vs. 44% (n=7); p=0.18 48-week follow-up - 83% (n=15) vs. 69% (n=11); p=0.43 proxy outcome:	

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	excluded if they had: History of renal insufficiency, defined as serum Cr > 1.5 times normal) Liver disease, defined as serum AST or ALT ≥2.5 times higher the upper limit of normal History of billiary cirrhosis Portal hypertension Allergic brochopulmonary aspergillosis (ABPA) B. Cepacia infection Lung transplantation Were on any antifungal			number of patients that experienced pulmonary exacerbations requiring hospitalization 24-week follow-up - 17% (n=3) vs. 19% (n=3); p=0.99 48-week follow-up - 22% (n=4) vs. 19% (n=3); p=0.99 Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status Not reported	

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	agents within 6 months before randomization			Quality of life (CFQ-R) (better represented by higher outcomes) 24-week follow-up - No significant differences in any of the 12 domains 24-week follow-up - Respiratory domain: 3.76 vs 4.77 points increase; MD -1.01 (p=0.87) Adverse events during the 24-week study period increased dyspnea: 2/18 vs 2/16 rash: 2/18 vs 1/16 hemoptysis: 2/18 vs 1/16	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				hyperglycaemia: 1/18 vs 0/16 flu-like illness: 3/18 vs 0/16 diarrhea: 0/18 vs 1/16 conjunctivitis: 0/18 vs 1/16 spontaneous pneumothorax: 1/18 vs 0/17 Emergence of resistant organisms/ antibiotic resistance Not reported	
Full citation Assael, B. M., Pressler, T., Bilton, D., Fayon, M., Fischer, R., Chiron, R., LaRosa, M., Knoop, C., McElvaney, N., Lewis, S. A., Bresnik, M., Montgomery, A. B., Oermann, C. M., Azli Active Comparator Study Group, Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial, Journal	Sample size N=273 randomized patients N=268 received treatment AZLI: n=136 TNS: n=132	Interventions Intervention Treatment: Inhaled aztreonam lysine (AZLI) Duration: 28 days Dose: 75 mg, (3 times/day)	Details Randomisation Method not reported Allocation concealment Open-label Blinding	Results Lung function (% change in FEV1 predicted from baseline) Across 3 treatment courses,	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: randomisation methods not reported, but group characteristics appear to be balanced Allocation concealment and blinding: open label study - patients and investigators were not blinded to treatment allocation Incomplete data: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of Cystic Fibrosis, 12, 130-40, 2013 Ref Id 398353 Country/ies where the study was carried out Belgium, Denmark, France, Germany, Ireland, Italy, UK, USA Study type Open-label, randomised, parallel-group trial Aim of the study To compare the efficacy and safety of AZLI to TNS, across three 28-day treatment courses. Study dates August 2008 to May 2010 Source of funding Gilead Sciences	233 patients (85.3%) completed the active-comparator period Mean use of distributed vials was 94.0% (AZLI) and 94.2% (TNS) Of 169 eligible patients, 133 (78.7%) entered the open-label extension period (AZLI: 68; TNS: 65), and 118 patients completed 3 AZLI courses (88.7%). Characteristics Patient characteristics were balanced between	Comparison Treatment: Inhaled tobramycin (TNS) Duration: 28 days Dose: 3000 mg (2 times/day) Control No treament Duration: 28 days	An independent, blinded data adjudication committee determined respiratory hospitalisations and respiratory events requiring additional antipseudomonal antibiotics. No further details reported. Data collection Collected at weeks 4, 12 and 20. No further details reported. Data analysis Statistical analyses were performed on the intent-to-treat (ITT) population:	mean actual change (SE): Aztreonam 2.05% (0.69) TNS -0.66% (0.72) Mean difference, aztreonam - TNS: Across 3 treatment courses: 2.70 (95% CI 0.98% to 4.43%, p=0.002) Mean difference at day 28 (week 4): 7.80 (95% CI 3.86% to 11.73%, p<0.001) Mean change from baseline at day 28 (week 4) (aztreonam 4.367, TNS 0.287) calculated	Selective reporting: supported by Gilead Sciences and continuous endpoints reported as the mean of weeks 4, 12 and 20 - final endpoint values are not reported Other: Other information Patients receiving additional antipseudomonal antibiotics at any point after randomisation could continue study treatments Included in SR Maiz 2013

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	treatment groups and reported separately for each group, overall: Mean age 25.5 years (SD 9.0) 50% male Mean FEV1% predicted 52.3 (SD 15.1) Inhaled colistin use in previous year 38.4% Aztreonam use at baseline 64.9% Dornase alfa use at baseline 68.3% Inhaled tobramycin use in previous year: >83 days, 85.1%		randomized patients receiving ≥1 dose of AZLI/TNS The primary non-inferiority endpoint (change in FEV1%) was assessed with an analysis of covariance (ANCOVA) model with terms for treatment, baseline FEV1% predicted (continuous variable), and inhaled tobramycin use in previous year (≥84, b84 days) The primary superiority endpoint was the average least- square means from	from relative change from baseline Time to next pulmonary exacerbation Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB Aztreonam 52/136 (38.2%) TNS 76/132 (57.6%) p=0.002 Proxy outcome: number of patients that experienced pulmonary exacerbations requiring hospitalization	

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	Inclusion criteria ≥6 years of age documented CF diagnosis PA-positive sputum culture within the previous 3 months FEV1 ≤75% predicted at screening Additional antipseudomonal AB could be administered for symptoms consistent with the diagnosis of acute pulmonary exacerbation Patients receiving additional antipseudomonal antibiotics at any point		Weeks 4, 12, and 20 visits, based on a mixed-effect model repeated measures (MMRM) analysis method outlined by Siddiqui, which included terms for treatment, baseline FEV1% predicted (continuous variable), inhaled tobramycin use (≥84, b84 days), visit, and treatment/visit interaction	Aztreonam 40/136 TNS 58/132 p=0.044 Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status Weight, relative change from baseline at Week 24 (end of active-comparator period), b %, adjusted mean (SE): Aztreonam 0.58 (0.41) TNS 0.06 (0.43) p=0.289 Quality of life CFQ-R respiratory	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	after randomization could continue study treatments Exclusion criteria Patient using additional TNS during the active-comparator period			symptoms scale, change from baseline score, b adjusted mean (SE): Week 4 (after course 1; AZ: n= 131; TNS: n= 131): aztreonam: 8.2 (1.7) TNS 2.6 (1.7) p= 0.005 Average across 3 courses (Weeks 4, 12, 20; Aztreonam: n= 131; TNS: n= 131) Aztreonam 6.3 (1.5) TNS 2.2 (1.5) p= 0.019 Adverse events	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Chest discomfort Aztreonam 14/136 (10.3%) TNS 13/132 (9.8%) Cough aztreonam 96/136 (70.6%) TNS 104/132 (78.8%) Headache aztreonam 29/136 (21.3%) TNS 27/132 (20.5%) Vomiting aztreonam 14/136 (10.3%) TNS 14/132 (10.6%) Dyspnoea aztreonam 31/136 (22.8%) TNS 21/132 (15.9%) Haemoptysis	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				aztreonam 31/136 (22.8%) TNS 21/132 (15.9%) Emergence of resistant organisms/ antibiotic resistance Log10 PA CFU/g sputum, change from baseline, b adjusted mean (SE) Week 4 (after course 1; AZLI: n= 88; TNS: n= 94) Aztreonam −0.60 (0.23) TNS −0.34 (0.23) p= 0.330 Average across 3 courses (Weeks 4, 12, 20; AZLI: n= 97; TNS: n= 97)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				aztreonam −0.55 (0.19) TNS 0.32 (0.19) p= 0.295	
Full citation Chuchalin, A., Csiszer, E., Gyurkovics, K., Bartnicka, M. T., Sands, D., Kapranov, N., Varoli, G., Monici Preti, P. A., Mazurek, H., A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection: a double-blind, placebo-controlled, multicenter study, Paediatric Drugs, 9 Suppl 1, 21-31, 2007 Ref Id 330572 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.
Full citation Elphick, H. E., Southern, K. W., Antifungal therapies for allergic bronchopulmonary aspergillosis	Sample size na Characteristics	Interventions Intervention Antifungal treatments,	Details na	Results No studies were identified for	Limitations AMSTAR score: 11/11 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD002204, 2014 Ref Id 365540 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To evaluate the effectiveness of antifungal interventions for the treatment of allergic bronchopulmonary aspergillosis (ABPA) in people with CF Study dates Most recent search 17 March 2014 Source of funding Not reported	na Inclusion criteria na Exclusion criteria na	including major treatments such as: oral azoles nebulised amphotericin Comparison No treatment Placebo Different dosages		inclusion in this review.	
Full citation Galeva,I., Konstan,M.W., Higgins,M., Angyalosi,G., Brockhaus,F., Piggott,S., Thomas,K., Chuchalin,A.G., Tobramycin inhalation powder manufactured by improved process in cystic fibrosis: the randomized EDIT trial, Current Medical Research and Opinion, 29, 947-956, 2013 Ref Id	Sample size TIP vs. placebo ITT efficacy population: 32 vs. 30 safety population: 30 vs. 32 (2 patients in TIP were	Interventions TIP 112mg or placebo twice daily, as capsules administered via the T-326 dry powder inhaler	Details Randomisation Using a validated autmated system and startified by age and screening FEV1% predicted	Results Lung function (% change in FEV1 predicted from baseline) Mean absolute change (SE) from	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk Allocation concealment: low risk Blinding: low risk Incomplete data: low risk Selective reporting: sponsored by Novartis Other: small sample size leading to an under powered study Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
310612 Country/ies where the study was carried out Bulgaria, Estonia, Latvia, Lithuania, Romania, Russia, Egypt, India Study type Double-blind, placebo-controlled randomised phase III trial Aim of the study To evaluate the efficacy and safety of tobramycin inhalation powder (TIP) in people with CF aged 6 to 21 years. Study dates June 2009 to May 2011 Source of funding Sponsored by Novartis Pharma AG, who were responsible for the design of the study and analysis of the data and in collaboration with the authors, interpreted and presented the data for this report	misallocated) completed: 29 vs. 30 Characteristics TIP vs. placebo female 70.0% vs. 59.4% mean (SD) FEV1% predicted 61.8 (17.5) vs. 63.1 (18.7) mean age (SD), years 12.9 (4.3) vs. 12.9 (4.7) The most frequently used medications were mucolytics (80% vs. 81%) and enzyme preparations (70% vs. 91%)		Allocation concealment Blinding details provided Blinding Blinding was maintained through matched packaging, laeling, schedule of administration and outer appearance of drug and device Data collection During each visit, lung function was measured using at least 3 acceptable forced expiratory maneuvers Spirometry data was transferred to a central site where an over-read was	baseline to day 29 analysed as randomised: TIP 4.9 (1.6) placebo 0.5 (1.7) p= 0.0496 Time to next pulmonary exacerbation Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring	If patients requiring treatment with antipsedudomonal antibiotics other than the study drug for signs and/or symptoms of a pulmnary exacerbation, they were required to withdraw from the study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Males and females aged 6 to 21 years with a diagnosis of CF confirmed by at least 1 clinical feature of CF plus sweat chloride test >60mEq/L, known mutations in each CF transmembrane conductance regulator (CFTR) gene or abnormal nasal transepithelial potential difference FEV1 at screening >24 and <81% of normal predicted		conducted to ensure inclusion only of acceptable data where quality standards were met Sputum and serum samples were collected on days 1 and 29 Supplementary appendix provides more details on data collection including that for safety assessments for the incidene and severity of adverse events Data analysis Aample size of 100 estimated to provide 90%	hospitalisation Hospitalistion due to respiratory events occurred in on patient in the placebo arm Eradication of the specified organism from sputum/airway cultures Clearance rates for PA at day 29 TIP 41.4% placebo 0% Supression, change in PA sputum density log10 CFU/G TIP 1.2 (0.3) n=29 placebo 0.0 (0.3) n=26 p= 0.002	

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	values for age, sex and height positive sputum or throat culture for P.A within 6 months of screening positive sputum culture for P.A at the screening visit Exclusion criteria Any previous exposure to TIP Any inhaled antipseudomonal antibiotics within 4 months prior to screening Any systemic antipsedomonal antibiotics within 28 days prior to		power to detect a treatment difference of 11% mean relative change in FEV1% predicted from baseline to day 29 at a 2 sided 5% significance level, assuming a SD of 16% and dropout rate <10% All efficacy analysis performed on ITT population and safety analysis on safety population Missing day 29 values were imputed with discontinuation visit measurement or the	Nutritional status Not reported Quality of life Not reported Adverse events Minor any TIP 8/29 (27.6%) placebo 11/26 (42.3%) Auditory impairment TIP 3/29 (10.3%) placebo 2/26 (7.7%) Cough TIP 5/29 (17.2%) placebo 0/26 (0%) Major, any TIP 1/29 (3.4%) placebo 1/26 (3.8%)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	study drug administration Loop diurectics within 7 days of first study drug admiistration Positive cultures for B.cepacia within 2 years prior to screening or at screening hemoptysis >60ml at any time within 30 days of study drug administration aminoglycoside hypersensitivty or adverse reaction to inhaled antibiotics serum creatine ≥2 mg/dl		baseline value (hence a change of 0 if no post baseline measure existed) ANCOVA was used to analyse the primary endpoint (relative change in FEV1% predicted from baseline to day 29) using screening FEV1% (<50 and ≥50 predicted) and age (<13 and ≥13 years) as factors, ANCOVA methods also used for change in sputum density of PA and absolute FEV1%	Emergence of resistant organisms/ antibiotic resistance Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	blood urea nitrogen ≥40 mg/dl abnormal urinalysis		predicted change		
Full citation Hodson, M. E., Gallagher, C. G., Govan, J. R., A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis, European Respiratory Journal, 20, 658-64, 2002 Ref Id 331052 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.
Full citation Jensen, T., Pedersen, S. S., Garne, S., Heilmann, C., Hoiby,	Sample size See Cochrane	Interventions See Cochrane SR Ryan 2011	Details See Cochrane	Results See Cochrane	Limitations See Cochrane SR Ryan 2011 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
N., Koch, C., Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection, Journal of Antimicrobial Chemotherapy, 19, 831-8, 1987 Ref Id 331175 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011		SR Ryan 2011	SR Ryan 2011	None.
Full citation Konstan,M.W., Flume,P.A., Kappler,M., Chiron,R., Higgins,M., Brockhaus,F., Zhang,J., Angyalosi,G., He,E., Geller,D.E., Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial, Journal of Cystic Fibrosis, 10, 54-61, 2011 Ref Id 239390	Sample size See Tappenden 2013 Characteristics See Tappenden 2013 Inclusion criteria	Interventions See Tappenden 2013	Details See Tappenden 2013	Results See Tappenden 2013	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk Allocation concealment: unclear risk Blinding: unclear risk Incomplete data: low risk Selective reporting: low risk Other: study funded by Novartis OVERALL: Moderate risk of bias , Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	See Tappenden 2013 Exclusion criteria				Allocation concealment: unclear risk Blinding: unclear risk Incomplete data: low risk Selective reporting: low risk Other: study funded by Novartis OVERALL: Moderate risk of bias Other information
Full citation Konstan, M. W., Geller, D. E., Minic, P., Brockhaus, F., Zhang, J., Angyalosi, G., Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial, Pediatric Pulmonology, 46, 230-8, 2011 Ref Id 361387 Country/ies where the study was carried out 38 centres: Bulgaria, Lithuanua, Serbia, Argentina, Brazil, Chile, Mexico, US Study type Randomised, double-blind, placebo-controlled trial Aim of the study To assess the efficacy and safety of tobramycin inhalation powder formulation for treating CF patients with P.aeruginosa infection	Sample size TIP vs. placebo Randomised: 46 vs. 49 Completed cycle 1: 39 vs. 40 Modified intention-to-treat: 29 vs. 32 (18 patients excluded due to results of sensitivity interim analysis, see other information for details) Characteristics	Interventions cycle 1 (of 3) was double-blind and placebo-controlled with patients randomised 1:1 to tobramycin inhalation powder (TIP, 112mg) or placebo both administered twice daily via the T-326 inhaler during cycle 1 (28 days) patients received TIP (4 capsules 28mg inhaled twice daily) or matching	Details Randomisation Method not reported Allocation concealment Placebo drug described in detail, but no further details provided Blinding Described as double-blind, but no further details provided	Results Lung function (% change in FEV1 predicted from baseline) TIP vs Placebo: 13.3 (95% CI: 5.31, 21.28) Time to next pulmonary exacerbation Not reported Eradication of the specified organism from	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk Allocation concealment: unclear risk Blinding: high risk Incomplete data: high risk Selective reporting: low risk Other: study funded by Novartis OVERALL: High risk of bias Other information After cycle 1, based on fulfilment of the pre-defined stopping criteria (statistically significant benefit of TIP over placebo) the Data Monitoring Committee recommended the trial be terminated early After reviewing spirometry data, the Data Monitoring Committee recommended the trial be terminated early again as 10 TIP treated and 8 placebo treated patients should be excluded from the interim analysis due to unacceptable calibration of the spirometer or unacceptable FEV1 data quality

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Study dates September 2005 to February 2007 Source of funding Funded by Novartis	TIP (n=46) vs. placebo (n=49) mean (SD) age, years 13.4 (4.42) vs. 13.2 (3.91) male n(%) 19 (41.3%) vs. 23 (46.9%) caucasian n(%) 37 (80.4%) vs. 43 (87.8%) mean (SD) FEV1% predicted* 54.7 (18.89) vs. 58.5 (20.03) * excluding patients from Latin America sites with potential spirometry quality concerns (n=32 vs. n=37) Inclusion criteria	placebo capsules after completing cycle 1, all patients received open-label TIP for 2 additional cycles (2x 28 days)	Data collection Planned interim analysis discussed in detail. Spirometry measurements and susceptabilti y also described. No further detail on data collection methods reported. Data analysis sample size of 140 patients (70 per group) was estimated to provide 90% power at 2-sided 0.05 significance level to detect a treatment difference of	sputum/airway cultures Not reported Nutritional status Not reported Quality of life Not reproted Adverse events During cycle 1 (TIP vs. placebo) cough 6 (13.0%) vs. 13 (26.5%) productive cough 1 (2.2%) vs. 4 (8.2%) hemoptysis 1 (2.2%) vs. 1 (2.0%) headache 1 (2.2%) vs. 3 (6.1%) any serious adverse event 6.5% vs. 14.3%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	CF patients aged 6 to 21 years FEV1 25 to 80% predicted based on Knudson criteria Positive sputum or throat culture for P.aeruginosa within 6 months of screening and a positive sputum culture for P.aeruginosa at the screening visit Exclusion criteria Positive cultures for B.cepacia within 2 years prior to screening or at screening		11% in mean (20% SD) relative change in FEV1% predicted in cycle 1 primary efficacy measure (relative change in FEV1% from baseline to day 28) was based on the MITT population primary measure assessed using ANCOVA with factors of treatment, baseline FEV1% predicted, age and region included in the model all other efficacy measures used the all-	Emergence of resistant organisms/ antibiotic resistance Sputum density of both non-mucoid and mucoid phenotypes of P.aeruginosa TIP vs. placebo: mean decrease (SD) non-mucoid: 1.91 (2.54) vs. 0.15 (0.68) log10CFU/g mucoid: 2.61 (2.53) vs. 0.43 (1.05) log10CFU/g Mortality 1 placebo patient died, they took their last	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	hemoptysis >60 cc at any time within 30 days of study drug administration aminoglycoside hypersensitivity or adverse reaction to inhaled antibiotics serum creatine ≥2 mg/dl blood urea nitrogen ≥40 mg/dl or abnormal urinalysis (≥2+ proteinuria) received inhaled antipseduomonal antibiotics within 28 days prior to study drug administration and loop		treated population all final analysis based on observed data with no imputation performed for missing data	treatment on day 8 during cycle 1 and discontinued due to a pulmonary exacerbation the next day	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	diuretics within 7 days of study drug administration Note: if patients required treatment with antipseudomonal antibiotics other than study drug for signs and/or symptoms of a pulmonary exacerbation, they were required to withdraw from the study				
Full citation Lenoir, G., Antypkin, Y. G., Miano, A., Moretti, P., Zanda, M., Varoli, G., Monici Preti, P. A., Aryayev, N. L., Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pseudomonas aeruginosa, Paediatric Drugs, 9 Suppl 1, 11-20, 2007 Ref Id 331327 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011				
Full citation Lo, D. K., Hurley, M. N., Muhlebach, M. S., Smyth, A. R., Interventions for the eradication of meticillin-resistant Staphylococcus aureus (MRSA) in people with cystic fibrosis, Cochrane Database of Systematic Reviews, 2, CD009650, 2015 Ref Id 398687 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To evaluate the effectiveness of antimicrobial treatment regimens	Sample size na Characteristics na Inclusion criteria na Exclusion criteria na	Interventions Intervention Any combination of topical, inhaled, oral or IV antimicrobials to eradicate MRSA Comparison Placebo Standard treatment No treatment	Details na	Results No trials were identified for inclusion in this review.	Limitations AMSTAR: 11/11 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
to eradicate meticillin-resistant S. Aureus (MRSA) in people with CF and all disease severities. Study dates Searches up to 4 September 2014 Source of funding National Institute for Health Research, UK					
Full citation McCoy, K. S., Quittner, A. L., Oermann, C. M., Gibson, R. L., Retsch-Bogart, G. Z., Montgomery, A. B., Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis, American Journal of Respiratory & Critical Care Medicine, 178, 921-8, 2008 Ref Id 331480 Country/ies where the study was carried out Study type Aim of the study THIS STUDY GOES IN THE NMA. DO I NEED TO EXTRACT DATA IN STAR? Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Murphy, T. D., Anbar, R. D., Lester, L. A., Nasr, S. Z., Nickerson, B., VanDevanter, D. R., Colin, A. A., Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease, Pediatric Pulmonology, 38, 314-20, 2004 Ref Id 361511 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations Other information
Full citation Ramsey, B. W., Dorkin, H. L., Eisenberg, J. D., Gibson, R. L., Harwood, I. R., Kravitz, R. M., Schidlow, D. V., Wilmott, R. W., Astley, S. J., McBurnie, M. A., et al.,, Efficacy of aerosolized tobramycin in patients with cystic fibrosis, New England Journal of Medicine, 328, 1740-6, 1993	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 331798 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria See Cochrane SR Ryan 2011				
Full citation Ramsey, B. W., Pepe, M. S., Quan, J. M., Otto, K. L., Montgomery, A. B., Williams-Warren, J., Vasiljev, K. M., Borowitz, D., Bowman, C. M., Marshall, B. C., Marshall, S., Smith, A. L., Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group, New England Journal of Medicine, 340, 23-30, 1999 Ref Id 331799 Country/ies where the study was carried out Study type	Sample size See Cochrane SR Ryan 2011 Characteristics See Cochrane SR Ryan 2011 Inclusion criteria See Cochrane SR Ryan 2011 Exclusion criteria	Interventions See Cochrane SR Ryan 2011	Details See Cochrane SR Ryan 2011	Results See Cochrane SR Ryan 2011	Limitations See Cochrane SR Ryan 2011 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Study dates Source of funding	See Cochrane SR Ryan 2011				
Full citation Remmington, T., Jahnke, N., Harkensee, C., Oral anti-pseudomonal antibiotics for cystic fibrosis, Cochrane Database of Systematic Reviews, 7, CD005405, 2016 Ref Id 537710 Country/ies where the study was carried out Study type Cochrane SR Aim of the study To determine the benefits or harms, or both, of oral anti-pseudomonal antibiotic therapy for people with CF who are colonised with P. aeruginosa in two clinical settings: treatment of a pulmonary exacerbation: and long-term treatment of chronic respiratory tract infection Study dates Date of last search: 08 July 2016. Source of funding No sources of support supplied	Sample size Sheldon 1993 40 randomised 31 completed the trial Characteristics Sheldon 1993 Mean age (sd) of 15 participants in the active treatment group: 28.3 years (6.06 years) Mean age (sd) of 16 participants in the placebo group: 24.9 years (5.15 years) Sex: active treatment	Interventions Sheldon 1993 Ciprofloxacin (500 mg) tds or an identical placebo for 10 days every 3 months for 4 courses	Details Sheldon 1993 Double-blind RCT (generation of allocation sequence & allocation concealment both graded as 'adequate') Parallel design Single centre The trial had a power of 80%for detecting a real difference of 200ml in the improvement of FEV1 between the groups significant at the 5% level.	Results Sheldon 1993 Ciprofloxacin vs. placebo Lung function (% change in FEV1 predicted from baseline) Not reported Time to next pulmonary exacerbation Not reported Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status,	Limitations Sheldon 1993 Adequate sequence generation? Yes. On enrolment into the trial participants were given consecutive trial numbers, which corresponded to the treatment group randomised before the study. Randomisation of treatment courses was arranged prior to the start of the trial in blocks of 4: 2 each for treatment and placebo Allocation concealment? Yes. Treatment courses were prepared by Bayer, none of the staff involved with the trial had knowledge of the treatment allocated to each participant Blinding? Unclear. Clinician/person delivering treatment: yes. Participants: yes Outcome assessor: unclear (see below). Described as double-blinded "None of the staff involved in the study had knowledge of the treatment allocated to each patient" Incomplete outcome data addressed? Unclear. 9 withdrawals, all described. 5 participants receiving CPX were withdrawn for the following reasons: poor compliance (2), heart-lung transplant (1), death (1), nausea & anorexia (1) 4 participants receiving placebo were withdrawn for the following reasons: poor compliance (2), death (1), desire to become pregnant (1) Free of selective reporting? No. Study protocol not available. All outcomes listed as beingmeasured at clinic visits were described in full in the results section of the paper for baseline and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	group: 13 males, 2 females; placebo group: 10 males, 6 females Country: UK Inclusion criteria Cochrane criteria: Ran domised or quasi-randomised controlled trials comparing any dose of oral anti-pseudomon al antibiotics, to other combination s of inhaled, oral or intravenous antibiotics, or to placebo or usual treatment for pul monary exacerbation s and long-			mean (SD) weight kg 55.7 (11.4) N=15 vs. 51.3 (11.6) N=16 MD 4.4 (95% CI -3.7 to 12.5) Quality of life Not reported Adverse events, n/N Gastrointest inal 2/20 vs. 0/20, RR 5.00 (95% CI 0.26 to 98.00) Emergence of resistant organisms/ antibiotic resistance Isolation of antibiotic resistant strains P.aeruginos a 10/15 vs. 5/16, RR 2.13 (0.95 to 4.80)	12 months. However, no data were presented for intermediate clinic visits Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	term treatment. Criteria applied in the included trials: Sheldon 1993 Eligible if over 18 years of age and chronically infected with P. aeruginosa Participants were excluded from the trial if they had P. aeruginosa resistant to CPX in their sputum culture immediately prior to entering the trial, renal insufficiency, an intention to become pregnant,			Isolation of antibiotic resistant strains S.aureus 4/15 vs. 6/16, RR 0.71 (0.25 to 2.03) Mortality 1/20 vs. 1/20, 1.00 (0.07 to 14.90)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	current treatment with theophyllines or a past history of poor compliance Exclusion criteria See inclusion criteria.				
Full citation Retsch-Bogart, G. Z., Quittner, A. L., Gibson, R. L., Oermann, C. M., McCoy, K. S., Montgomery, A. B., Cooper, P. J., Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis, Chest, 135, 1223-32, 2009 Ref Id 331839 Country/ies where the study was carried out Australia, Canada, New Zealand and USA Study type Randomised, double-blind, placebo-controlled trial Aim of the study	Sample size Randomised: aztreonam 80, placebo 84 Completed to day 28: aztreonam 73, placebo 65 Characteristics Placebo; aztreonam mean age (range): 31.7 (11-74); 27.4 (7-54) male: 45/84 (53.6%);	Interventions 75mg aztreonam, 52.5mg of lysine monohydrate, or placebo (5mg lactulose) both administered with an eFlow Electronic nebuliser (PARI) patients self-administered a short acting beta2-agonist before administering	Details Randomization Randomized 1:1. Web-based system using a central computer-generated randomization schedule, and stratified by baseline disease severity (FEV1 ≤ or ≥ 50%) and a block size of 4.	Results Lung function - FEV1 (L) change from baseline At week 4: aztreonam - placebo 0.102; calculated from relative change from baseline assuming baselines are same Time to next pulmonary	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk Allocation concealment: unclear, the process is not reported Blinding: unclear, the study indicates that it is double-blinded, but the process is not reported Incomplete data: high number of people discontinued treatment for a short trial: placebo 19/84, aztreonam 7/80 Selective reporting: supported by Gilead Sciences Other: none Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To evaluate the efficacy and safety of inhaled aztryonam lysine (AZLY) in patients with CF and chronic P. Aeruginosa infection. Study dates June 2005 to April 2007 Source of funding Gilead Sciences	48/80 (60.0%) dornase alfa use: 64%; 66% mean (SD) FEV1% predicted: 54.8 (14.0); 54.4 (13.4) mean (SD) CFQ-RRS: 60.9 (18.9); 60.5 (18.1) Inclusion criteria ≥6 years of age Confirmed CF diagnosis Moderate-to-severe lung disease (FEV1 ≥25% to ≤75% predicted) PA airway infection (documented at screening or twice within previous year,	the study medication at home	Allocation concealment Not reported Blinding Double-blinded, no details provided Data collection Physical examination at baseline; spirometry at every visit, before and 30' after any treatment. FEV1% predicted Knudson. Data analysis Sample size of 40 estimated to provide 77% power to detect an 8-point difference for change in	exacerbation Not reported Proxy outcome: number of patients that experienced pulmonary exacerbations requiring hospitalisation At 42 days: aztreonam 4/80; placebo 12/84 Eradication of the specified organism from sputum/airway cultures Adjusted MD in sputum PA density log10 CF/g at day 28: -1.453 (95%CI -2.1 to -0.8); p<0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	including once within the previous 3 months) without regard to PA susceptibility to aztreonam Ability to perform reproducible pulmonary function tests Exclusion criteria recent (ie, day -28 to screening) administration of inhaled, IV, or oral antipseudomonal antibiotics, azithromycin, or aerosolized hypertonic saline solution current oral corticosteroid use		CFQ-RRS assuming a SD of 20 and >90% power to detect a 9% difference in FEV1 assuming a SD of 12 with a two sided alpha 0.05 CFQ-R analysis used last observation carried forward Efficacy and safety analysis included all randomly assigned patients receiving one or more doses of aztreonam/placebo Continuous variables were analysed using	Nutritional status Weight, mean change %, at day 28: 1,1 (n=80) vs 0,1 (n=84); (95%CI 0.33 to 1.69); p=0.004 Quality of life (CFQ-R) (better represented by higher outcomes) AZLI group (n=80) vs placebo (n=84) Body Image:3.2 vs 1.0; p=0.327 Digestion: 2.2 vs 1.9; p=0.889 Eating: -3.6 vs 4.7; p=0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	equivalent to >10 mg of prednisone daily airway cultures yielding Burkholderia cepacia complex (previous 2 years) daily continuous oxygen supplementation or >2 L/min at night monobactam antibiotic hypersensitivity intolerance to inhaled short-acting beta2-agonists recent changes in antimicrobial, bronchodilator, antiinflammatory, or		analysis of covariance models with treatment as the fixed effect, disease severity ad baseline values were covariates	Emotional Functioning: 3.9 vs 1.3; p=0.005 Health Perceptions: 5.0 vs -4.8; p=0.001 Physical Functioning: 2.3 vs 6.9; p=0.001 Respiratory Symptom: -7.1 vs 2.6; p=0.001 Role/School: 2.1 vs 4.2; p=0.014 Social Functioning: 1.2 vs -3.6; p=0.248 Treatment Burden: 0.2 vs 3.1; p=0.177 Vitality: 3.6 vs 4.4; p=0.005 Weight: 4.7 vs 1.4; p=0.376	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	corticosteroid medications, or physiotherapy technique/schedule lung transplantation new findings on chest radiograph at screening or in the previous 90 days aspartate aminotransferase or alanine aminotransferase levels more than five times the upper limit of normal (at screening), or serum creatinine levels more than two times the upper limit of			Minor adverse events Cough, at 28 days (n/N): 28/80 vs. 25/84 Headache, at 28 days (n/N): 5/80 vs 10/84 Chest discomfort, at 28 days (n/N): 5/80 vs 4/84 Abdominal pain, at 28 days (n/N): 2/80 vs 6/84 Major adverse events Hemoptysis, at 28 days (n/N): 2/80 vs 6/84 Dyspnea, at 28 days (n/N): 5/80 vs 8/84	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	normal (at screening) pregnancy lactation in the opinion of the investigator, medical or psychiatric illness interfering with study participation. Patients were not permitted to use other antipseudomonal antibiotics or azithromycin during the study or during the 14-day follow-up period, unless required for the treatment of worsening symptoms.			Emergence of resistant organisms/ antibiotic resistance proxy: treatment-emergent persistent isolation of other organisms, 42 days follow-up S aureus (n/N): 2/74 vs 5/81 B cepacia (n/N): 0/74 vs 0/81 S maltophilia (n/N): 2/74 vs 0/81 A xylosoxidans (n/N): 1/74 vs 2/81	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ryan, G., Singh, M., Dwan, K., Inhaled antibiotics for long-term therapy in cystic fibrosis, Cochrane Database of Systematic Reviews, CD001021, 2011 Ref Id 331888 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The aim of this review is to identify the most effective inhaled antibiotic for long-term therapy in people with CF. Study dates Searches up to 31 January 2011 Source of funding Clinical Staff Education Fund, Sir Charles Gairdner Hospital (Australia)	Sample size 8 trials were included from this review 1 trial (McCoy 2008) evaluates Aztreonam 2 trials (Hudson 2002, Jensen 1987) evaluate Colistin 6 trials (Chuchalin 2007, Hudson 2002, Lenoir 2007, Murphy 2004, Ramsay 1993, Ramsay 1999) evaluate Tobramycin Characteristics	Interventions Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Chuchalin 2007 Intervention: Tobramycin 300mg (Bramitob®. Used a Pari LC Plus jet nebuliser and Pari Turbo Boy air compressor Comparison: placebo (saline solutionwith quinine hydrochloride solution) Study duration: 24 weeks (4 weeks 'on treatment'	Details Chuchalin 2007 Randomised Multicentre (21 sites across Hungary, Poland and Russia, parallel study Placebo-controlled Double-blind A 2:1 (tobramycin: placebo) allocation used Hodson 2002 Random allocation, stratified by age and centre Parallel design Open label Jensen 1987 Random allocation Parallel design	Results Where possible data was extracted from the Cochrane SR. The full copy of the study was checked for accuracy and completeness. Additional data extracted is marked with a * COMPARISON: AZTREONAM VS PLACEBO McCoy 2008 FEV1 FEV1% change from baseline to day 28: AZLI vs placebo	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual studies The RoB assessment has been taken from the SR. Chuchalin 2007 Adequate sequence generation: unclear (Randomised, but method not stated. Ratio tobramycin to placebo 2:1) Allocation concealment: unclear (not stated, multicentre) Blinding (all outcomes): yes (Double-blind, quinine hydrochloride added to placebo to mask taste) Incomplete data outcome (all outcomes): yes (247 randomised, 245 ITT analysis, 215 PP analysis. 232 completed the study, 6.1% drop out rate (tobramycin group 7 dropouts (4.3%), placebo group 8 dropouts (9.3%)). Reasons given) Free selective reporting: Unclear (Not clear if results formicrobiology are ITT or PP) Other bias: no (Supported by Chiesi Famaceutici SpA (Italy), MDS Pharma Services (France)) Hudson 2002 Adequate sequence generation: Unclear (Described as 'randomised'. Stratified by age groups in each centre) Allocation concealment: Unclear (Not stated) Blinding (all outcomes): No (Not used) Incomplete outcome data addressed (all outcomes): Yes (Figure of screened, randomised, treated, withdrawn, analysed ITT stated. 94% completed. Attrition rate 6%. Reasons given) Free of selective reporting: Yes (Outcome stated in methods section have been reported, although no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Chuchalin 2007 N: 247 randomised 245 included in ITT population M/F: 135 males, 110 females Diagnosis of CF + P. Aeruginosa Hodson 2002 N: 143 people screened, 17 screening failures 126 people randomised, 11 withdrew before treatment, 115 treated Gender: 45% males Age range: 7 - 50 years Exclusion: any anti-pseudomonal antibiotics within the	followed by 4 weeks 'off treatment') Hodson 2002 Intervention: Tobramycin 300 mg in 5 ml twice daily Comparison: Colistin 1MU in 3 ml in saline twice daily Duration: 28 days Pari LC plus (tobramycin) or Ventstream (colistin) nebuliser with CR50 compressor. Jensen 1987 Intervention: Colistin (1 million units), twice daily, raindrop nebuliser with 3.0 ml of solution. Comparison: placebo (normal	Double-blinded Placebo control Lenoir 2007 RCT Parallel design Multicentre (13 sites, 4 countries) Double-blind Placebo-controlled McCoy 2008 RCT Parallel design Multicentre (56 centres in USA) Double-blind Placebo controlled Ramsey 1993 Random allocation Cross-over design: 3-period cross-over design Double blinded	(6.3% (95% CI: 2.5-10.1)) Time to next exacerbation proxy outcome: frequency of one or more hospital admissions at 1 to 3 months: placebo 1/76; AZLI 6/135 Eradication of the organism Nutritional status Not reported Quality of life CFQ-R at 1 month (MD, SE): 5.01 (2.14) Adverse events minor AE - Voice alteration, at the end of	protocol was available for a more thorough assessment) Other bias: Unclear (Sponsor Pathogenesis Limited.) Jensen 1987 Adequate sequence generation: Unclear (Described as randomised, but method not stated) Allocation concealment? Unclear (Not stated) Blinding (all outcomes): Unclear (Reported as double-blind, but not stated who was blinded) Incomplete outcome data addressed (all outcomes): Yes (29/40 completed. Attrition rate 28%. Reasons given) Free of selective reporting: No (Tolerance, FEF, Shwachman score and nocturnal cough are partially reported so that data could not be included in a meta-analysis i.e. 'no significant difference'. No protocol was available for a more thorough assessment) Free of other bias: No (Uneven withdrawals; 2/20 in colistin group and 9/20 in placebo group. Mean baseline FEV1 71% predicted (colistin) and 79% predicted (placebo) in participants analysed) Lenoir 2007 Adequate sequence generation: Yes (Randomly assigned to 1 of 2 treatments according to randomisation list prepared in blocks of 4 participants) Allocation concealment: Unclear (Not stated. Multi-centre) Blinding (all outcomes): Yes (Double-blind, quinine hydrochloride added to placebo. Report stated investigators, co-investigators and nursing staff were blinded to the treatment randomized; participants presumed to be blinded. Tobramycin and matching placebo supplied in unit dose vials) Incomplete outcome data addressed (all outcomes): Yes (59 randomised, 59 ITT analysis, 56 PP analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous 14 days. Criteria for diagnosis abnormal sweat electrolytes, gene mutation Jensen 1987 N: 40 Gender: 20 males Age range: 7 - 35 years Diagnostic criteria for CF: not stated Chronic P. aeruginosa infection. Mean baseline FEV1 71% (SD 25) and 79% (SD 29) predicted in 2 treatment groups Lenoir 2007 N: 59 participants Gender: 32 males	saline), twice daily Duration of treatment: 3 months Lenoir 2007 Intervention: Tobramycin 300 mg (Bramitob®, t wice dail. Used Pari LC Plus nebuliser and Pari TurboBoy compressor. Comparison: placebo, twice daily Duration: 4 weeks followed by a 4-week run-out phase 4 weeks. McCoy 2008 Intervention: Aztreonam 75 mg, 2 or 3 times per day for 28 days Comparison: placebo (5mg lactose in 1 ml. 0.17%	Placebo control Ramsey 1999 Random allocation Parallel design Double blinded Placebo control Murphy 2004 Randomised Parallel group Open label Stratified by age and sex	the study (n/N): 2/135 vs 4/76 minor AE - Cough (n/N), at the end of the study: 43/135 vs 26/76 major AE - Haemotypsis, at the end of the study (n/N): 13/135 vs 7/76 major AE - Anaphylaxis, at the end of the study: none reported in any of the groups* Deaths: no deaths* Emergence of resistant organisms/ AB resistance Not reported	51 completed, 13.6% drop out rate (tobramycin group 1 drop out (3.4%), placebo group 7 dropouts (23.3%). Reasons given) Free of selective reporting: No (Some outcomes stated in the methods section were not reported in the results section, for example blood pressure, heart rate) Other bias: Unclear (Study sponsored & funded by Chiesi Farmaceutici (Italy)) McCoy 2008 Adequate sequence generation: unclear (states "randomly assigned" only) Allocation concealment: unclear (not stated) Blinding: unclear (indicates double blind, but not clear who's blinded) Incomplete data outcome: yes (211 participants started the study after the open-label phase started, and 173 finished the study, Reasons provided in the flowchart) Free selective reporting: no Other bias: unclear (authors used a composite endpoint "the need (symptoms) for additional AB") Ramsey 1993 Adequate sequence generation:Unclear (Described as randomised, stratified FEV1 groups in each centre) Allocation concealment: Unclear (Not described) Blinding (all outcomes): Unclear (Described as double blind, but not stated who. Used quinine to mask nebulised solutions adequately) Incomplete outcome data addressed (all outcomes): Yes (Intention-to-treat analysis stated with random exclusion to match numbers for crossover analysis. 66/71 completed. 5 withdrew from study. Attrition rate 6%. Reasons given) Free of selective reporting: No (Serum creatinine and auditory acuity only partially reported. 'The levels of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Age range: 6 to 30 years Diagnosed CF + P. aeruginosa McCoy 2008 N: 246 participant Gender: 121 males Age range: 7 to 65 years Documented diagnosis of CF + P. aeruginosa, 3 or more courses of tobramycin in previous year, FEV1 between 25 and 75% predicted. Ramsey 1993 N: 71 participants Gender: 37 male Mean age: 17.7 years, SD 1.25 years and	NaCl), 2 or 3 times per day Duration: 4 weeks Ramsey 1993 Intervention: Tobramycin 600 mg, 3-times daily Comparison: Placebo. 0.5 normal saline, 3-times daily Duration: 28 days, then cross-over for two 28-day periods Ultrasonic (Ultraneb 100/99) nebuliser with 30 ml solution and 200 inhalations Ramsey 1999 Intervention: Tobramycin 300 mg, twice daily. Pari LC plus nebuliser with 5 ml of solution and		COMPARISON: COLISTIN VS PLACEBO Jensen 1987 FEV1 mean (SD) % change in FEV1 (% predicted) at 1 to 3 months (90 days): placebo - 17.00 (11.00); nebulised colistin - 11.00 (6.00) mean (SD) final FEV1 (% predicted) at day 60: placebo 62.00 (25.00); nebulised colistin 63.00 (24.00) Time to next exacerbation	serum creatinine in all patients remained in the normal range throughout the study. No clinically important or statistically significant change occurred in auditory acuity in either study group') Other bias: No (Cross-over design. They examined for carry-over or period effects and a carry-over effect for FEV1 was reported. When tobramycin was used intermittently, an improvement in FEV1 did not return to baseline during four weeks off treatment. Sponsor CFF) Ramsey 1997 Adequate sequence generation: Unclear (Described as adaptive randomisation procedure, stratified by 7 criteria) Allocation concealment: Unclear (Not stated) Blinding (all outcomes): Unclear (Described as double blind, but not stated who. Used quinine to attempt to mask nebulised solutions adequately) Incomplete outcome data addressed (all outcomes): Yes (ITT analysis stated, 90%completed. Attrition rate 10%. 56 participants did not complete the study.) Free of selective reporting: No (FVC is only partially reported in the many journal articles for this study. Other results seemto be reported. No protocol was available for a more thorough assessment and there were multiple publications from this study) Other bias: Unclear (Some investigators are patent holders. Support NIH, CFF, FDA.) Murphy 2004 Adequate sequence generation? Unclear risk. Described as randomised, but no method described Allocation concealmnt? Unclear risk. Not described Blinding? High risk. Open label study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	16.6 years, SD 1.24 years CF diagnosed by sweat test Sputum culture of P. aeruginosa susceptible to tobramycin. Mean baseline FEV1 55% (SE 3.7) and 60% (SE 3.2) predicted in 2 treatment arms Ramsey 1999 N: 520 participants Gender: 54% male Age from six years, 54% 18 years or older Criteria for CF were CFF clinical	Pulmo-aide compressor. Comparison: placebo, 0.225 normal saline and 1.25 mg quinine, twice daily Duration: three 28-day on-off cycles Murphy 2004 Tobramycin 300 mg twice daily, alternating 4-weekly cycles for 56 weeks Method of nebulisation: Pari LC Plus jet nebulizer and Pulmo-Aide compressor		Not reported Eradication of the organism P. Aeruginosa was not eradicated from the sputum of any patient during 3-month the trial* Nutritional status Not reported Quality of life Not reported Adverse events Not explicitely reported Emergence of resistant organisms/ AB resistance No superinfecti on with with other colistin-	Incomplete outcome data addressed? Low risk. Planned sample size 400, 184 randomised, 63 completed 56 weeks. Attrition rate 65%. 88 sponsor requested withdrawals. Reasons given Free of selective reporting? High risk. Many outcomes were not fully reported, only stating a non-significant difference between groups, including number of missed school days and weight. Also for lung function measurements, although these were also shown graphically Free of other bias? High risk. Early termination for benefit. 63 of 181 randomised participants completed 56 weeks. Sponsor tobramycin manufacturer Chiron Corporation Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	practice guidelines All infected with P. aeruginosa. Baseline FEV1 25-75% predicted Murphy 2004 N: 184 52% male age 6-15 years 2 or more cultures of P.aeruginosa Inclusion criteria Chuchalin 2007 Diagnosis of CF + P. aeruginosa Hodson 2002 Exclusion included any anti-pseudomonal antibiotics within the			resistant microorganisms, including Ps. Cepacia, Serratia marcescens, Proteus mirabilis, Gram-positive organisms or fungi during 3-month the trial* Resistance to Colistin did not develop in any strain during 3-month the trial* No change in resistance pattern to other commonly used anti-pseudomonas treatments during 3-	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous 14 days Criteria for diagnosis abnormal sweat electrolytes, gene mutation Jensen 1987 Diagnostic criteria for CF not stated Chronic P. aeruginosa infection Lenoir 2007 Diagnosed CF + P. aeruginosa McCoy 2008 Documented diagnosis of CF + P. aerugi nosa, 3 or more courses of tobramycin in previous yea r, FEV1 betwe en 25 and			month the trial* COMPARIS ON: TOBRAMY CIN VS PLACEBO Chuchalin 2007 FEV1 mean (SD) FEV1% predicted at 24 weeks (adjusted for baseline): placebo 62.27 (1.42); tobi neb 68.65 (1.03) Time to next exacerbatio n proxy outcome: frequency of one or more hospital admissions over 3 months and up to 12	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	75% predicted Ramsey 1993 CF diagnosed by sweat test Sputum culture of P. aeruginosa susceptible to tobramycin Ramsey 1999 Criteria for CF were CFF clinical practice guidelines All infected with P. aeruginosa Baseline FEV1 25-75% predicted. Murphy 2004 2 or more cultures of P. aeruginosa			months: placebo 31/78, tobi neb 78/153 Eradication of the organism negative culture, at 4 weeks (n/N): 49/159 vs 12/84* negative culture, at 8 weeks (n/N): 23/159 vs 10/83* negative culture, at 20 weeks (n/N): 52/156 vs 13/79* negative culture, at 24 weeks (n/N): 38/159 vs 17/84* Nutritional status	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria See inclusion criteria			Patients treated with Tobramycin had greater mean weight gain at all visits ($p<0.01$)* bodyweight change from baseline to 24 weeks: significant increase in Tobramycin (95%CI 1.5 to 2.1) and placebo (95%CI 0.6 to 1.5) groups* BMI change from baseline to 20 weeks: significant increase in Tobramycin group (95%CI 0.3 to 0.6); no significant increase in placebo group*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				BMI at 20 weeks: significantly higher in the Tobramycin group (p<0.01)* Quality of life Not reported Adverse events patients with treatment-related AE during the 24 weeks study period (n/N): 25/161 vs 13/85* patients with serious AE during the 24 weeks study period (n/N): 17/161 vs 22/85* Deaths over during the 24 weeks study period	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(n/N): 1/61 vs 2/86 Emergence of resistant organisms/ AB resistance frequency of Tobramycin-resistant P. Aeruginosa at 24 weeks (end of the study) (n/N): 35/153 vs 14/78 Lenoir 2007 FEV1 mean (SD) % change in FEV1 (% predicted), at 1 to 3 months from baseline (4 weeks): placebo 2.53 (18.50); tobi neb 16.11 (13.50) mean FEV1 (%	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				predicted) at the end of treatment: placebo 62.3 (20.9); tobi neb 73.8 (19.5) Time to next exacerbation not reported Eradication of the organism negative culture at 4 weeks (end of treatment) (n/N): 10/29 vs 5/30* negative culture at 6 weeks follow-up (n/N): 3/29 vs 3/30* Nutritional status weight-change (kg) at 4 weeks (end of treatment) (mean, SD):	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0.39 (0.9) vs 0.16 (0.9) Quality of life not reported Adverse events treatment-related AE during the 4-week treatment phase (n/N): 3/29 vs 7/30* serious AE during the 4-week treatment phase (n/N): 1/29 vs 3/30* deaths during the 4-week treatment phase (n/N):0/29 vs 1/30* Emergence of resistant organisms/ AB resistance not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Ramsey 1999 FEV1 change in FEV1 from baseline to week 20: placebo -2.0%; tobi neb 10.0%; p<0.001 Time to next exacerbation proxy outcome: frequency of one or more hospital admissions over 3 months and up to 12 months (20 weeks): placebo 117/232; tobi neb 95/232 Eradication of the organism proxy: density of P.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Aeruginosa in sputum samples at week 20 (log10 CFU per gram): -0.8 vs +0.3 * Nutritional status not reported Quality of life not reported Adverse events minor AE - auditory impairment, at 24 weeks (end of the study) (n/N): 0/152 vs 0/148 minor AE - tinnitus, at 24 weeks (end of the study) (n/N): 8/258 vs 0/262 minor AE - voice alteration, at 24 weeks	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(end of the study) (n/N): 33/258 vs 17/262 major AE - Haemotypsis, at 24 weeks (end of the study) (n/N): 69/258 vs 81/262 major AE - pneumothorax, at 24 weeks (end of the study) (n/N): 1/258 vs 4/262 Deaths at 24 weeks (end of the study) (n/N): 0/258 vs 4/262 Emergence of resistant organisms/ AB resistance frequency of Tobramycin-resistant P. Aeruginosa at 24 weeks (end of the	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				study) (n/N): 51/223 vs 17/218 frequency of new isolates of drug resistant B. Cepacia (n/N): 0/258 vs 0/262 frequency of new isolates of drug resistant S. Maltophilia (n/N): 3/258 vs 1/262 frequency of new isolates of drug resistant A. xylosidans (n/N): 1/258 vs 1/262 frequency of new isolates of drug resistant Aspergillus (n/N): 4/196 vs 20/193 Ramsey 1993 FEV1	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				mean % change in FEV1 (% predicted), at 1 to 3 months (28 days adjusted for baselin): tobi neb vs. placebo: 4.32 (95% CI: 1.6, 7.04) Time to next exacerbation proxy: pulmonary exacerbations at 4 weeks: placebo 2/35; tobi neb 5/36 Eradication of the organism proxy: density of P. Aeruginosa at 4 weeks (CFU/g, log10) (mean±SE; 95%CI): -	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1.87±0.30 (2.47 to -1.27) (n=58)* Nutritional status not reported Quality of life not reported Adverse events minor AE - auditory impairment, during the 42-week observation period (n/N): 0/36 vs 0/35 Emergence of resistant organisms/ AB resistance emergence of P. Cepacia: 3 infected during the 4-week study period, no significant differences	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				between Tobramycine and placebo periods (p>0.7)* emergence of P. Maltophilia: 10 infected during the 4-week study period, no significant differences between Tobramycine and placebo periods (p>0.7)* emergence of resistant P. Aeruginosa strains (n/N): 10/71 during the4-week study period, no significant differences between Tobramycine and	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				placebo periods (p>0.5)* Murphy 2004 FEV1 not reported Time to next exacerbation proxy: number of subjects hospitalised for respiratory reasons (52 weeks); control 23/90 vs tobi neb 10/91; p=0.011* Eradication of the organism not reported Nutritional status not reported Quality of life not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse events not repoted Emergence of resistant organisms/ AB resistance not reported COMPARISON: INHALED TOBRAMYCIN VS COLISTIN Hudson 2002 FEV1 mean % change in FEV1 (% predicted), at 4 weeks of AB therapy (mean, SD): see NMA data extraction table Time to next exacerbation not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Eradication of the organism proxy: change in sputum P. Aeruginosa density Log10 cfu mL-1, at 4 weeks of AB therapy (mean, SD) (ITT population): -0.86±1.43 (n=50) vs -0.60±1.651 (n=50)* proxy: change in sputum P. Aeruginosa density Log10 cfu mL-1, at 4 weeks of AB therapy (mean, SD) (microbiologically evaluable population): -0.79±1.35 (n=42) vs -	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				0.47±1.53 (n=37)* Nutritional status not reported Quality of life not reported Adverse events minor AE - increased cough, by the end of the 4-week study period (n/N): 5/53 vs 11/62 minor AE - increased sputum, by the end of the 4-week study period (n/N): 6/53 vs 8/62 minor AE - dyspnea, by the end of the 4-week study period (n/N): 5/53 vs 7/62 minor AE - pharyngitis,	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				by the end of the 4-week study period (n/N): 7/53 vs 3/62 major AE - patients with ≥1 serious AE by the end of the 4-week study period (n/N): 8/53 vs 7/62* Emergence of resistant organisms/ AB resistance no evidence of development of highly tobramycin-resistant P. Aeruginosa in either group at 8 weeks follow-up*	
Full citation Schuster, A., Haliburn, C., Doring, G., Goldman, M. H., Freedom Study, Group, Safety, efficacy and convenience of	Sample size N=380 (Safety population: patients who	Interventions Intervention Treatment: inhaled	Details Randomization No detail given	Results Lung function	Limitations Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: unclear risk (the process is not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study, Thorax, 68, 344-50, 2013 Ref Id 331950 Country/ies where the study was carried out Europe (Countries not specified) Study type Open-label RCT Aim of the study To investigate whether colistimethate formulated as a dry powder inhaler can be as effective as inhaled antibiotics given via a nebuliser in controlling chronic P aeruginosa infection in cystic fibrosis patients. Study dates March 2003 - October 2007 Source of funding Funding for the study was provided by Forest Laboratories UK, Dartford	received at least one dose of medication) Treatment (CDPI) n=187 [One patient dropped out immediately following randomisation and did not receive treatment] Comparison (TIS) n=193 N=374 (ITT population) Treatment (CDPI) n=183 Comparison (TIS) n=191 Characteristics (Treatment vs. comparison) Age (mean±SD): 21.3±9.72 vs. 20.9±9.30 -	colistimethate sodium (CDPI) Formulation: capsules Duration: 24-weeks Dosing: 1.6625 MU twice daily Comparison tobramycin inhaler solution (TIS) Formulation: solution for inhalation Duration: three 28-day cycles Dosing: twice-daily 300 mg/5 ml	Allocation concealment Described as “centrally randomized”, but no details given Blinding Described as open-lable Data collection Patients underwent study assessments at baseline and at 24 weeks.	CDPI - TIS: -0.98 (95% CI: -2.74, 0.86) Time to next pulmonary exacerbation Not reported Eradication of the specified organism from sputum/airway cultures Not reported Nutritional status Not reported Quality of life Not reported Adverse events Safety population reported. CDPI	Allocation concealment: unclear risk (the process is not reported) Blinding: low risk (This study is described as open-label RCT) Incomplete data: Low risk (ITT performed) Selective reporting: low risk (All the outcomes stated in the methods and the study protocol are appropriately reported) Other: low risk (None detected) OVERALL QUALITY: moderate risk of bias Other information (+) multicentre prospective RCT and large sample size (+) outcome assessor were blinded to the treatment being given (+) ITT performed (-) unclear randomization (-) no blinded Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Total: 21.1 ±9.49 Male (%): 56.3 vs 52.9 - Total:54.5 FEV1 % predicted (mean±SD): 49.14±14.895vs. 50.80 ±6.336 - Total: 49.78±11.980 Inclusion criteria 66 European CF centres Confirmed CF diagnoses ≥ 6 years of age Chronically colonised with P aeruginosa infection, defined as at least 2 positive sputum cultures within the last 12			(n=186) vs. TIS (n=193) n(%) Withdrawals due to an AE 22 (11.8) vs. 5 (2.6) Mild AE 159 (85.0) vs. 165 (85.5) Moderate AE 123 (65.8) vs. 97 (50.3) Severe AE 48 (25.7) vs. 13 (6.7) Cough 193 (15.7) vs. 123 (10.3) Dyspnoea 81 (6.6) vs. 98 (8.2) Productive cough 62 (5.0) vs. 76 (6.4)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	months prior to the first day of trial medication Stable clinical condition: no evidence of a current acute respiratory exacerbation at the pre-run visit Exclusion criteria Patients were excluded if they had: presence of Burkholderia cepacia complex infection in the airways, ongoing pulmonary exacerbation (based on a modified Fuchs definition) sensitivity to any study medication				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Sheldon, C. D., Assoufi, B. K., Hodson, M. E., Regular three monthly oral ciprofloxacin in adult cystic fibrosis patients infected with Pseudomonas aeruginosa, Respiratory Medicine, 87, 587-93, 1993 Ref Id 331984 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Remmington 2016 Characteristics See Cochrane SR Remmington 2016 Inclusion criteria See Cochrane SR Remmington 2016 Exclusion criteria See Cochrane SR Remmington 2016	Interventions See Cochrane SR Remmington 2016	Details See Cochrane SR Remmington 2016	Results See Cochrane SR Remmington 2016	Limitations See Cochrane SR Remmington 2016 Other information
Full citation Tappenden,P., Harnan,S., Uttley,L., Mildred,M., Carroll,C., Cantrell,A., Colistimethate sodium powder and tobramycin	Sample size EAGER trial N randomised: 553	Interventions EAGER trial Intervention Tobramycin DPI	Details EAGER trial Design: RCT, open label	Results EAGER trial Note: Data is presented as	Limitations QUALITY OF THE TA AMSTAR: 11/11 QUALITY OF THE INDIVIDUAL STUDIES

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
powder for inhalation for the treatment of chronic Pseudomonas aeruginosa lung infection in cystic fibrosis: systematic review and economic model, Health Technology Assessment (Winchester, England), 17, v-xvii, 2013 Ref Id 322218 Country/ies where the study was carried out UK Study type Health Technology Assessment Aim of the study To evaluate the clinical effectiveness and cost-effectiveness of Colismethate sodium dry powder of inhalation (DPI) and Tobramycin DPI for the treatment of chronic P. Aeruginosa lung infection in CF. Study dates Searches up to March 2011 Source of funding The National Institute for Health Research Health Technology Assessment programme. Individual study funding: EAGER trial: Novartis Pharmaceuticals COLO/DPI/02/06: Forest Laboratories	Intervention: 329 Control: 224 Number withdrawn before medication: 36 Intervention: 21 Control: 15 Number withdrawn after medication or lost to follow-up: 121 Intervention: 83 Control: 38 COLO/DPI/02/06 N randomised: 380 Intervention: 187 Control: 193 Number withdrawn before	Device: T-326 Inhaler Dose:112 mg twice daily Schedule: 28 days on treatment followed by 28 days off treatment Comparison Tobramycin inhalation solution Device: PARI LC Plus jet nebuliser Dose: 300 mg/5 ml twice daily Schedule: 28 days on treatment followed by 28 days off treatment COLO/DPI/02/06 Intervention Colistimethate sodium DPI	Duration: 24 weeks 127 centres, 15 countries COLO/DPI/02/06 Design: RCT, open label Duration: 24 weeks 66 centres in EU countries, Russia and the Ukraine COLO/DPI/02/05 Design: RCT, open label with cross-over Duration: 8 weeks Three centres in the UK	Tobramycin inhalation powder vs Tobramycin inhalation solution Lung function see NMA table Number of people experiencing 1 or more exacerbations see NMA table Time to next pulmonary exacerbation not reported Eradication of the specified organism from sputum/airway cultures mean change in P. Aeruginosa sputum density	The quality was assessed using 3 tools. Data was extracted for the CRD criteria only. EAGER trial Random allocation: yes Adequate concealment: yes Similar groups at the outset: yes Blinding: no Unexpected imbalance in drop-outs? were they explained or adjusted for? yes/ no All outcomes reported?: no ITT analysis? was this appropriate? appropriate methods used? yes/ yes/ no COLO/DPI/02/06 Random allocation: unclear Adequate concealment: yes Similar groups at the outset: yes Blinding: no Unexpected imbalance in drop-outs? were they explained or adjusted for? yes/yes All outcomes reported?: no ITT analysis? was this appropriate? appropriate methods used? yes/ yes/ yes COLO/DPI/02/05 Random allocation: yes Adequate concealment: unclear Similar groups at the outset: unclear Blinding: no Unexpected imbalance in drop-outs? were they explained or adjusted for? no/ na

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
COLO/DPI/02/05: Forest Laboratories	medication: 7 Intervention: not reported Control: not reported Number withdrawn after medication or lost to follow-up: 53 Intervention: 32 Control: 21 COLO/DPI/02/05 N randomised: 16 Number withdrawn before medication: 0 Number withdrawn after medication or lost to follow-up: 3	Device: Turbospin device Dose: 125 mg twice daily Schedule: continuous treatment Comparison Tobramycin inhalation solution Device: LC Plus jet nebuliser Dose: 300 mg/5 ml twice daily Schedule: 28 days on treatment followed by 28 days off treatment COLO/DPI/02/05 Intervention Colistimethate sodium DPI Device: Turbospin device		log10 CFU, at 4 weeks: -1.76 (SD 1.96) (n=308) vs −1.32 (SD 2.03) (n=209) mean change in P. Aeruginosa sputum density log10 CFU, at 20 weeks: -1.61 (SD 2.03) (n=308) vs −0.77 (SD 1.78) (n=209) negative P. Aeruginosa culture: 11.6% vs 9.9% Nutritional status Not reported Quality of life Not reported Adverse events	All outcomes reported?: yes ITT analysis? was this appropriate? appropriate methods used? yes Other information Full report: http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0011/94295/FullReport-hta17560.pdf

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Characteristics EAGER trial Age (mean, SD): 26 (11.4) vs 25 (10.2) Gender, male (%): 55.5% vs 55.0% FV1% predicted: 53 (SD 14.2; SE 0.81) vs 53 (SD 15.9; SE 1.11) Chronic macrolide use: 60.7% vs 59.8% No differences in chronic macrolide use, or use of anti-pseudomonal txt before trial COLO/DPI/02/06	Dose: 125 mg twice daily Schedule: continuous treatment Comparison Colistimethate sodium solution Device: NR Dose: 2 MU twice daily Schedule: continuous treatment		mild or moderate AE (%/N): 73.4%/308 vs 68,5%/209 serious AE (%/N): 27,4%/308 vs 29,2%/209 productive cough (n/N): 56/308 vs 41/209 dyspnea (n/N): 48/308 vs 26/209 vomiting (n/N): 19/308 vs 12/209 headache (n/N): 35/308 vs 25/209 haemoptysis (n/N): 40/308 vs 26/209 Emergence of resistant organisms/	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Age (mean, SD): 21.3(9.72) vs 20.9 (9.30) Gender, male (%): 56.3% vs 53.2% FV1% predicted: 51.76 (SE 1.02) vs 50.82 (SE 0.99) Mucolytics: 74.3% vs 79.1% Macrolides: 49.7% vs 51.3% COLO/DPI/02/05 Age (mean, SD): 37.5% were ≥8 and <13 years; 62.5% were ≥13 Gender, male (%): NR FV1% predicted:			antibiotic resistance P. aeruginosa isolates (all phenotypes) with MIC > 8 µg/ml (resistant) at baseline 68/308 (22.1%) P. aeruginosa isolates (all phenotypes) with MIC ≤ 8µg/ml (susceptible) at baseline 240/308 (77.9%) MIC > 8 µg/ml at the end of cycle 3 19.1% Increased MIC of tobramycin against P. aeruginosa from baseline to day 28 of cycle 3: Fourfold or	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	75.92 (SE 11.86) vs 79.51 (SE 7.707) All patients were on nebulised colistimethate sodium Patients were permitted to continue with pre-existing non-antipseudomonal CF medications Inclusion criteria INCLUSION CRITERIA FOR THE TA Study design: RCTs. Population: people aged ≥ 6 years with CF and chronic P. aeruginosa pulmonary infection. (Children of			greater increase: 67/199 (33.7%); Twofold or greater increase: 97/199 (48.7%); (unclear which numbers relate to which group) COLO/DPI/02/06 Note: Data is presented as Colistimethate sodium dry powder vs Tobramyin nebulised solution Lung function see NMA table Number of people experiencing 1 or more	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	< 6 years of age were excluded from the assessment, as they are subject to different treatment regimens, methods of assessment of lung function differ, and licensing has not been sought for this age group). Interventions: Studies assessing the effectiveness of colistimethate sodium DPI or tobramycin DPI Comparators: the comparator intervention or other			exacerbations see NMA table Time to next pulmonary exacerbation Time to next acute exacerbation (mean): 63.70 vs 59.30 days proxy: time to first additional anti-pseudomonal treatment (mean number of days): 55.28 (43.2) (n=183) vs 51.79 (41.9) (n=191) days Eradication of the specified organism from sputum/airway cultures Not reported	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	antipseudomonal antibiotics for nebulised inhalation, including, as a minimum, colistimethate sodium for nebulised inhalation or tobramycin for nebulised inhalation. Outcomes: rate and extent of microbial response; lung function; respiratory symptoms; frequency and severity of acute exacerbations; HRQoL; and AEs of treatment; complianc INCLUSION CRITERIA FOR THE INDIVIDUAL STUDIES			Nutritional status BMI change from baseline to week 24 (mean, SD): 0.08 (0.78) (n=183) vs 0.17 (0.89) (=191) kg Quality of life Physical (adj mean change from baseline to week 24): 0.26 vs −1.56; p=0,353 Vitality (adj mean change from baseline to week 24): 0.86 vs −1.40; p=0.293 Emotion (adj mean change from baseline to week 24): 2.23 vs	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	EAGER trial Age: ≥ 6 years old FEV1: > 25% to < 75% predicted Patients with chronic P. aeruginosa infection (sputum or throat cultures positive for P. aeruginosa within 6 months of screening and at baseline) COLO/DPI/02/0666 Age: ≥ 6 years old FEV1 > 25 to < 75% predicted Patients with chronic P. aeruginosa infection (≥2 sputum or			0.47; p=0.244 Eating (adj mean change from baseline to week 24): 0.48 vs 0.66; p=0.925 Treatment burden (adj mean change from baseline to week 24): 5.62 vs 2.75; p=0,091 Health perceptions (adj mean change from baseline to week 24): 0.25 vs −2.71; p=0.159 Social (adj mean change from baseline to week 24): 3.10 vs 0.92; p=0.153	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	throat cultures positive for P. aeruginosa within 6 months of screening) Run-in inclusion criteria: patients to receive ≥2 nebulised tobramycin on/off cycles immediately prior to randomisation Non-smokers or a past smoker who had not smoked within the past 12 months Patients who, on first day of trial medication administration (Visit 1), had ≥ 28			Body image (adj mean change from baseline to week 24): 7.83 vs 5.98; p=0.385 Role (adj mean change from baseline to week 24): 0.65 vs 1.87; p=0.607 Weight (adj mean change from baseline to week 24): 0.88 vs −1.93; p=0.461 Respiratory (adj mean change from baseline to week 24): 2.99 vs 3.51; p=0.756 Digestion (adj mean change from baseline to	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	days but ≤ 35 days off tobramycin COLO/DPI/02/0566 Age: ≥ 8 years old FEV1 > 25% prediction Non-smokers or a past smoker who had not smoked within the past Exclusion criteria EXCLUSION CRITERIA FOR THE TA studies based on animal models; preclinical and biological studieS non-RCTs editorials, opinion pieces;			week 24): 5.06 vs 2.89; p=0.077 Adverse events study drug-related AE at 24 weeks (n/N): 153/187 vs 90/193 patients withdrawn due to serious AE at 24 weeks (n/N): 22/187 vs 5/193 productive cough at 24 weeks (n/N): 38/187 vs 44/193 chest discomfort at 24 weeks (n/N): 26/187 vs 34/193 dyspnea at 24 weeks (n/N):	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	reports published as meeting abstracts only where insufficient details were reported studies published only in languages other than English studies in which the population was not restricted to CF, unless data for just this population was presenteD			49/187 vs 52/193 vomiting at 24 weeks (n/N): 6/187 vs 8/193 haemoptysis at 24 weeks (n/N): 20/187 vs 13/193 Emergence of resistant organisms/ antibiotic resistance not reported COLO/DPI/ 02/05 Note: Data is presented as Colistin inhalation powder vs Colistin inhalation solution Lung function see NMA table Number of people	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				experiencing 1 or more exacerbations see NMA table Time to next pulmonary exacerbations not reported Eradication of the specified organism from sputum/airway cultures not reported Nutritional status not reported Quality of life not reported Adverse events dyspnea at 8 weeeks follow-up (n/N): 3/16 vs 4/15 vomiting at 8 weeeks follow-up	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				(n/N): 2/16 vs 0/15 productive cough at 8 weeeks follow-up (n/N: 2/16 vs 1/15 chest discomfort a t 8 weeeks follow-up (n/N): 4/16 vs 2/15 Emergence of resistant organisms/ antibiotic resistance not reported	
Full citation Trapnell, B. C., McColley, S. A., Kissner, D. G., Rolfe, M. W., Rosen, J. M., McKevitt, M., Moorehead, L., Montgomery, A. B., Geller, D. E., Phase, F. T. I. Study Group, Fosfomycin/tobramycin for inhalation in patients with cystic fibrosis with pseudomonas airway infection, American Journal of Respiratory & Critical Care Medicine, 185, 171-8, 2012 Ref Id	Sample size N=119 GROUP A (placebo) n=40 [Completing study: 32– for safety or tolerability: 6] GROUP B (FTI 80/20 mg) n=38 [Completing	Interventions Intervention Treatment: Fosfomycin/to bramycin for inhalation (FTI) A) 160/40 mg or B) 80/20 mg Formulation: solution for inhalation Duration: 4-weeks	Details Randomizati on Randomizati on used an interactive voice recognition system (code generated by Gilead Sciences) (p 2 additional	Results Lung function (see NMA abstraction tables) Time to next pulmonary exacerbatio n Not reported Eradication of the specified	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk Allocation concealment: unclear risk (the process is not reported) Blinding: low risk Incomplete data: unclear risk (On one hand missing outcome data are balanced in numbers between groups, on the other hand there is insufficient information about attrition/exclusions to permit judgement of yes or not)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
332159 Country/ies where the study was carried out US Study type Double-blind, placebo-controlled, multicentre RCT - (NMA only) Aim of the study To evaluate the safety and efficacy of a 28-day course of Fosfomycin/tobramycin for inhalation (FTI) versus placebo, following a 28-day, open-label, run-in course of aztreonam for inhalation solution (AZLI). Study dates June 2008 to January 2010: patient enrolment 2012: results publication Source of funding Funding from Food and Drug Administration grant 1R01FD003016-01 and National Institutes of Health General Clinical Research Center grants M01 RR00188 and M01 RR10733	study: 35– for safety or tolerability: 1] GROUP C (FTI 160/40 mg) n=41 [Completing study: 34 – for safety or tolerability: 8] Characteristics (A vs B vs C) Age (mean±SD): 31±8.8 vs. 35±10.9 vs. 31±10.1 - Total: 32 ±10.1 Male (%): 68% vs 55% vs 49% - Total: 57% FEV1 % predicted (mean±SD): 48±13.6 vs. 50±13.4 vs. 48±14.6 - Total: 49 ±13.8	Dosing: twice daily Comparison Placebo: 5/10 mg lactose monohydrate powder 7.3/14.6 mg NaCl; 2/4 mL 0.17% NaCl diluent Formulation: solution for inhalation Duration: 4-weeks All patients were treated with AZLI (75 mg aztreonam; 52.5 mg lysine monohydrate; reconstituted in 1 mL 0.17% NaCl diluent) during the 28-day, open-label, run-in period.	file) and it was stratified by disease severity at screening (FEV1 ≤ 50% and FEV1 > 50% predicted). Allocation concealment No details given Blinding Described as double-blinded Data collection Patients underwent study assessments at baseline and at 4 weeks.	organism from sputum/airway cultures Not reported Nutritional status Not reported Quality of life Not reported Adverse events Not reported	Selective reporting: low risk (All the outcomes stated in the methods and the study protocol are appropriately reported) Other: low risk (None detected) OVERALL QUALITY: moderate risk of bias Other information (+) multicentre prospective RCT and large sample size (+) double blinded (-) unclear allocation concealment (-) relatively short timeframe Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria 33 US CF centres Confirmed CF diagnoses ≥18 yr of age FEV1 ≥ 25%, and FEV1 ≤ 75% predicted at screening colonised with P aeruginosa infection able to perform reproducible pulmonary function tests Exclusion criteria Patients were excluded if they had: administration of intravenous, oral, or inhaled				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	antipseudomonal antibiotics or changes in azithromycin regimen within 14 days prior to screening, or changes in antimicrobial, bronchodilator, corticosteroid, hypertonic saline, or dornase alfa medications, or physiotherapy technique or schedule within 7 days				
Full citation Wainwright,C.E., Quittner,A.L., Geller,D.E., Nakamura,C., Wooldridge,J.L., Gibson,R.L., Lewis,S., Montgomery,A.B., Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa, Journal of	Sample size Placebo vs. aztreonam Treated: 81 vs. 76 Completed study: 81 vs. 76	Interventions Aztreonam: 75mg aztreonam, 52.5mg lysine monohydrate Placebo: 5mg lactulose, 7.3mg NaCl	Details Randomization Stratified by age (6–13, 14–17, ≥18 years) and geographic region (North	Results Aztreonam vs. placebo Lung function - % change in FEV1 predicted	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: described Allocation concealment: method not reported Blinding: double blind, but method not reported Incomplete data: low risk Selective reporting: low risk, but sponsored by Gildead Sciences

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cystic Fibrosis, 10, 234-242, 2011 Ref Id 310385 Country/ies where the study was carried out Australia, USA Study type Double-blind, multicentre, placebo-controlled RCT Aim of the study To evaluate Aztreonam for inhalation solution as antipseudomonal treatment in people with CF with P. Aeruginosa. Study dates June 2008 to June 2009 Source of funding Sponsored by Gilead Sciences, Inc and by NIH General Clinical Research Center grants M01 RR00400, M01 RR10733, and M01 RR00188	Completed treatment: 79 vs. 71 Characteristics Demographic characteristics were well balanced between treatment arms The majority of patients were 6–17 years of age (56.7%) Most patients were receiving dornase alfa (81.5%) and pancreatic enzymes (88.5%) at baseline Patients had received a mean of 2.9 courses of TIS in the previous year; 65.0% of patients	Both diluted in 0.17% saline and self-administered with the investigtional eFlow PARI electronic nebuliser Patients self-administered a short acting bronchodilator before each study drug dose	America, Australia; randomization code generated by Gilead Sciences) Allocation concealment Nnot reported Blinding Double-blind, details not reported Data collection Not reported Data analysis For the primary efficacy analysis (CFQ-R) treatment effect was assessed by a parametric analysis of covariance (ANCOVA), treatment and age group were	from baseline Relative change (SE) in FEV1% predicted from baseline to day 28: 0.29 (0.85) (n=76) vs. -2.5 (0.82) (n=81), p=0.021 Mean change from baseline (0.27 vs. -2.37) calculated from relative change from baseline (therefore SD not calculable) Number of people with ≥1 exacerbations Not reported Time to next pulmonary exacerbation	Other: none Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	had received≥1 course. Inclusion criteria ≥ 6 years old documented CF FEV1 > 75% P. Aeruginosa present in expectorated sputum or throat swab culture samples at screening or documented in two samples within the previous 12 months (1 of them 3 months before screening) ≥ 2 of the following chronic and/or intermittent CF symptoms for ≥ 28		fixed effects and baseline CFQ-R RSS score was a covariate Analysis of other continuous variables used similar ANCOVA models, with respective baseline values as covariates Analyses included all randomly assigned patients receiving at least 1 dose of study drug Sample size of 140 would provide >89% power to detect a 10-point difference between groups in mean change from baseline at	Not reported Eradication of the specified organism from sputum/airway cultures Log10 PA CFUs in sputum, adj mean change (SE) at 28 days: -1.4 (0.36) (n=76) vs -0.14 (0.36) (n=81), p=0.016 Nutritional status Not reported Quality of life (CFQ-R) (better represented by higher outcomes) CFQ-R RSS, adj mean change (SE) at 28 days: 3.22 (1.7) (n=75) vs	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	days before baseline with no worsening of symptoms within 7 days before baseline no need for for inmediate antipseudomonal AB treatment of an impending recommendation able to perform reproductible pulmonary function test Exclusion criteria known hypersensitivity to monobactam AB inability to tolerate short-acting bronchodilators		day 28 on the CFQ-R RSS using a 2 sided 0.05 level test assuming a standard deviation of 17.5	1.41 (1.6) (n=81) CFQ-R PF, adj mean change (SE) at 28 days: 1.8 (1.6) (n=76) vs -0.69 (1.5) (n=80) CFQ-R RSS, adj mean change (SE) at 42 days: 3.0 (1.7) (n=75) vs 2.9 (1.7) (n=81) Adverse events Patients experiencing 1 or more AE: 59/76 vs 62/81 Mild to serious AE (in pt experiencing AE): 54/59 vs 59/62 txt related cough (n/%): 31 (38.3) vs. 35	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	lung transplantation history previous enrollment in an Aztreonam trial			(46.1); p=0.337 txt related productive cough (n/%): 13 (16.0) vs 18 (23.7); p=0.316 txt related respiratory tract congestion (n/%): 6 (7.4) vs 11 (14.5); p=0.201 Serious AE (n/N): 9/76 vs 3/81 Emergence of resistant organisms/ antibiotic resistance There was no evidence for persistent increases in the isolation of Burkholderia spp., Stenotrophomonas	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				maltophilia, Achromobacter xylosoxidans, Aspergillus spp., or S. aureus.	
Full citation Flume, P. A., Clancy, J. P., Retsch-Bogart, G. Z., Tullis, D. E., Bresnik, M., Derchak, P. A., Lewis, S. A., Ramsey, B. W., Continuous alternating inhaled antibiotics for chronic pseudomonal infection in cystic fibrosis, Journal of Cystic Fibrosis, 15, 809-815, 2016 Ref Id 566978 Country/ies where the study was carried out US Study type Double-blind, randomised trial, phase 3 Aim of the study To evaluate the safety and efficacy of a continuous alternating therapy (CAT) regimen with aztreonam for inhalation solution (AZLI; Cayston®; Gilead Sciences, Inc.) and nebulised tobramycin (TIS;	Sample size Randomised: CAT 43, tobi neb 47 Treated in comparative phase: CAT 42, tobi neb 46 Characteristics Mean (SD) age, years 28.4 (11.4); p=0.96 Female 51/88 (58%); p=1.00 Mean FEV1% predicted (SD) 50.0 (16.4); p=0.96 CFQ-R RSS score at Day	Interventions Enrolled subjects received TIS 300 mg twice daily (BID) during a 28-day run-in phase (Fig. supplement). This was followed by randomization to a 24-week comparative phase Subjects received 3 cycles of 28-days of double-blind AZLI or placebo (1:1 randomization) alternating with 28-days	Details Randomisation Eligible subjects were stratified by disease severity (forced expiratory volume at 1 s [FEV1] ≤50% or N50% predicted at Day 1) and number of acute respiratory exacerbations (1, 2, or ≥3; determined by the investigator) that required hospitalizatio	Results Lung function (% change in FEV1 predicted from baseline) Values at Weeks 4, 12, and 20 were averaged, adjusted mean (SE) change from baseline: CAT 1.37 (0.67); tobi neb 0.04 (0.66) Mean difference (95% CI) 1.33 (−0.55, 3.20)	Limitations Risk of bias (Cochrane Risk of Bias tool) Sequence generation: low risk - subjects stratified Allocation concealment: not reported Blinding: insufficient detail Incomplete data: unclear Selective reporting: sponsored by Gildead Sciences and not all final results available for continuous outcomes - reported as the mean of weeks 4, 12 and 20 Other: recruitment finished early leading to an under powered study Other information PDEs were defined as a change or worsening from baseline of 1 or more documented signs or symptoms (decreased exercise tolerance or appetite; increased cough, sputum, or chest congestion; or other signs/symptoms) associated with use of IV or non-study inhaled antibiotics and were verified by a blinded independent adjudication committee review of the data.

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TOBI; Novartis) in adult and pediatric subjects with CF and chronic pulmonary PA infections Study dates December 2012 to January 2015 Source of funding Sponsored by Gilead Sciences who was involved in the study design, in the collection, analysis, and interpretation of the data	1, mean (SD): CAT 60.2 (18.3); tobi neb 64.2 (15.2); p=0.16 Azithromycin use at Day 1 and/or during comparative phase, yes, n (%): CAT 34 (81.0); tobi neb 36 (78.3); p=0.80 Inclusion criteria ≥6 years of age with documented evidence of PA lung infection, FEV1 25–75% predicted received ≥1 course of IV antibiotic treatment for a pulmonary exacerbation within the	of open-label TIS TIS was delivered using an LC Plus nebulizer (PARI Respiratory Equipment) and Pulmo-Aide compressor (DeVilbiss Healthcare) AZLI was delivered using the eFlow Nebulizer System (PARI) Placebo was lactose monohydrate and sodium chloride, reconstituted with the same diluent used for AZLI (0.17% w/v sodium chloride solution) A short acting bronchodilator	n or IV antibiotic use during the previous year. Allocation concealment Method not reported Blinding The blinded adjudication committee identified respiratory-related hospitalisations. No further details reported Data collection Secondary endpoints were collected after each course. The blinded adjudication committee identified respiratory-related hospitalizatio	p=0.16 Time to next pulmonary exacerbation Median (95% CI) time to first PDE: CAT 175.0 days (76.0, NE) tobi neb 140.0 days (90.0, NE) hazard ratio [95% CI]: 0.89 [0.50, 1.59] p = 0.71 Proxy outcome: number of patients that experienced pulmonary exacerbations requiring oral or IV AB CAT 21/42, tobi neb 26/46	

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	previous 12 months stable regimen for any chronic use of azithromycin, bronchodilators, dornase alfa, hypertonic saline, and/or corticosteroid medications, or physiotherapy techniques/ regimen for ≥28 days before enrollment subjects receiving any antibiotic treatment, including AZLI or TIS, were eligible for screening, including	was administered before every AZLI/ placebo dose	ns. No further details reported. Data analysis Planned enrollment was 250 subjects; 125 subjects per arm would provide ≥85% power to declare superiority of alternating AZLI/TIS to placebo/TIS in the PDE rate, assuming an approximately 40% difference in exacerbation rate (2-sided, 0.05 level) Efficacy analyses included all randomized subjects (intention-to-treat), safety analyses	Eradication of the specified organism from sputum/airway cultures Adjusted mean changes from baseline sputum PA density after each course during the comparative treatment phase were small (0.36 to −0.55 log10 CFU/g). Differences between treatment groups were not statistically significant. Nutritional status Not reported	

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	subjects receiving intermittent, continuous, or continuous alternating aerosolized antibiotic treatment, but subjects could not be receiving any antibiotics (except azithromycin) when starting the TIS run-in phase Exclusion criteria subjects who used b50% of expected vials during any course of antibiotics were discontinued from study treatment complete inclusion/exc		included treated subjects. A family alpha-spending rule controlled the Type 1 error rate of 0.05, with the primary endpoint analysis serving as the gatekeeper and secondary endpoints tested sequentially (α = 0.05) based on the closed testing procedure The primary endpoint (rate of PDEs) was analyzed by negative binomial regression with an offset	Quality of life Adjusted mean (SE) CFQ-R RSS scores averaged from Weeks 4, 12, and 20 from baseline: C AT +1.00 (1.74); tobi neb −2.06 (1.63); p = 0.21 Adverse events CAT vs. tobi neb cough 32/42 (76.2%) vs. 20/42 (71.7%) dyspnea 13/42 (31.0%) vs. 24/46 (52.2%) grade 2 or 4 severity 13/42 (31.0%) vs.	

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	lusion criteria are listed in the online supplement		parameter accounting for follow-up time (2-sided, 0.05 level) Average changes from baseline FEV1% predicted and CFQ-R RSS scores were analyzed using an MMRM method, with terms for baseline value, previous exacerbations (1, 2, ≥3), treatment, visit, and treatment-by-visit interaction	14/46 (30.4%) grade 1 or 2 severity 21/42 (50.0%) vs. 24/46 (52.2%) Emergence of resistant organisms/ antibiotic resistance Methicillin-resistant S. aureus (MRSA) present at ≥1 visit: tobi neb 18/45 (40.0%); CAT 11/42 (26.2%)	
Full citation Ahmed, Treatment for chronic Staphylococcus aureus chest infection in people with cystic	Sample size Characteristics	Interventions Intervention Any combinations	Details No trials were identified for	Results	Limitations Other information

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fibrosis. http://www.cochrane.org/CD011581/CF_treatment-chronic-staphylococcus-aureus-chest-infection-people-cystic-fibrosis, 2016 Ref Id 590834 Country/ies where the study was carried out Study type Cochrane systematic review Aim of the study To assess the evidence regarding the effectiveness of long-term antibiotic treatment regimens for chronic infection with methicillin-sensitive Staphylococcus aureus (MSSA) infection in people with cystic fibrosis and to determine whether this leads to improved clinical and microbiological outcomes. Study dates Date of the last search of the Group's Cystic Fibrosis Trials Register: 03 March 2016. Source of funding	Inclusion criteria Exclusion criteria	of topical, inhaled, oral or intravenous (IV) antimicrobials used with the objective of suppressive therapy for chronic infection with S. aureus Comparison Placebo No treatment.	inclusion in this review.		
Full citation Forest Laboratories UK. , A randomised, open label study to compare the efficacy and safety of a dry powder formulation of	Sample size See Tappenden 2013	Interventions See Tappenden 2013	Details See Tappenden 2013	Results See Tappenden 2013	Limitations See Tappenden 2013 Other information

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inhaled colistimethate sodium and nebulised TNSFI (tobramycin nebuliser solution for inhalation, TOBI®) in cystic fibrosis patients with Pseudomonas aeruginosa lung infection. Final protocol no: COLO/DPI/02/06. , 2011 Ref Id 590835 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Characteristics See Tappenden 2013 Inclusion criteria See Tappenden 2013 Exclusion criteria See Tappenden 2013				
Full citation Forest Laboratories UK. , Colistimethate sodium powder for inhalation for the treatment of Pseudomonas lung infection in cystic fibrosis – Forest submission to NICE. COLO/DPI/02/05. , 2011 Ref Id 590836 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Tappenden 2013 Characteristics See Tappenden 2013 Inclusion criteria See Tappenden 2013 Exclusion criteria	Interventions See Tappenden 2013	Details See Tappenden 2013	Results See Tappenden 2013	Limitations See Tappenden 2013 Other information

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	See Tappenden 2013				