G.12 Immunomodulatory agents

Review question: What is the effectiveness of immunomodulatory agents in the management of lung disease, for example corticosteroids, azithromycin?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Auerbach, H. S., Williams, M., Kirkpatrick, J. A., Colten, H. R., Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis, Lancet, 2, 686-8, 1985 Ref Id 365436 Country/ies where the study was carried out USA Study type	Sample size See Cochrane SR Cheng 2015 Characteristics See Cochrane SR Cheng 2015 Inclusion criteria See Cochrane SR Cheng 2015 Exclusion criteria See Cochrane SR Cheng 2015	Interventions See Cochrane SR Cheng 2015	Details See Cochrane SR Cheng 2015	Results See Cochrane SR Cheng 2015	Limitations See Cochrane SR Cheng 2015 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT Aim of the study Study dates Source of funding					
Full citation Balfour-Lynn, I. M., Klein, N. J., Dinwiddie, R., Randomised controlled trial of inhaled corticosteroids (fluticasone propionate) in cystic fibrosis, Archives of Disease in Childhood, 77, 124-30, 1997 Ref Id 361047 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Balfour-Lynn 2012 Characteristics See Cochrane SR Balfour-Lynn 2012 Inclusion criteria See Cochrane SR Balfour-Lynn 2012 Exclusion criteria See Cochrane SR Balfour-Lynn 2012	Interventions See Cochrane SR Balfour-Lynn 2012	Details See Cochrane SR Balfour-Lynn 2012	Results See Cochrane SR Balfour-Lynn 2012	Limitations See Cochrane SR Balfour-Lynn 2012 Other information None.
Full citation Balfour-Lynn, I. M., Lees, B., Hall, P., Phillips, G., Khan, M., Flather, M., Elborn, J. S., Cf Wise Investigators,	Sample size See Cochrane SR Balfour-Lynn 2012 Characteristics See Cochrane SR Balfour-Lynn 2012	Interventions See Cochrane SR Balfour-Lynn 2012	Details See Cochrane SR Balfour-Lynn 2012	Results See Cochrane SR Balfour-Lynn 2012	Limitations See Cochrane SR Balfour-Lynn 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Multicenter randomized controlled trial of withdrawal of inhaled corticosteroids in cystic fibrosis, American Journal of Respiratory & Critical Care Medicine, 173, 1356-62, 2006 Ref Id 330332 Country/ies where the study was carried out UK Study type RCT Aim of the study Study dates Source of funding	Inclusion criteria See Cochrane SR Balfour-Lynn 2012 Exclusion criteria See Cochrane SR Balfour-Lynn 2012				
Full citation Clement, A., Tamalet, A., Leroux, E., Ravilly, S., Fauroux, B., Jais, J. P., Long term effects of azithromycin in patients with cystic fibrosis: A double blind, placebo controlled trial,	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Thorax, 61, 895-902, 2006 Ref Id 330590 Country/ies where the study was carried out France Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Southern 2012				
Full citation De Boeck, K., De Baets, F., Malfroot, A., Desager, K., Mouchet, F., Proesmans, M., Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients?, European Journal of Pediatrics, 166, 23-8, 2007 Ref Id 365519 Country/ies where the study was carried out Belgium Study type	Sample size See Cochrane SR Balfour-Lynn 2012 Characteristics See Cochrane SR Balfour-Lynn 2012 Inclusion criteria See Cochrane SR Balfour-Lynn 2012 Exclusion criteria See Cochrane SR Balfour-Lynn 2012	Interventions See Cochrane SR Balfour-Lynn 2012	Details See Cochrane SR Balfour-Lynn 2012	Results See Cochrane SR Balfour-Lynn 2012	Limitations See Cochrane SR Balfour-Lynn 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT Aim of the study Study dates Source of funding					
Full citation Eigen, H., Rosenstein, B. J., FitzSimmons, S., Schidlow, D. V., A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic Fibrosis Foundation Prednisone Trial Group, Journal of Pediatrics, 126, 515-23, 1995 Ref Id 365535 Country/ies where the study was carried out Study type Aim of the study Study dates Source of funding	Sample size See Cochrane SR Cheng 2015 Characteristics See Cochrane SR Cheng 2015 Inclusion criteria See Cochrane SR Cheng 2015 Exclusion criteria See Cochrane SR Cheng 2015	Interventions See Cochrane SR Cheng 2015	Details See Cochrane SR Cheng 2015	Results See Cochrane SR Cheng 2015	Limitations See Cochrane SR Cheng 2015 Other information None.
Full citation Equi,A., Balfour-Lynn,I.M., Bush,A., Rosenthal,M., Long term azithromycin in	Sample size See Cochrane SR Southern 2012 Characteristics	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
children with cystic fibrosis: A randomised, placebo-controlled crossover trial, Lancet, 360, 978-984, 2002 Ref Id 310518 Country/ies where the study was carried out UK Study type RCT Aim of the study Study dates Source of funding	See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012				Included in NMA only.
Full citation Greally, P., Hussain, M. J., Vergani, D., Price, J. F., Interleukin-1 alpha, soluble interleukin-2 receptor, and IgG concentrations in cystic fibrosis treated with prednisolone, Archives of Disease in Childhood, 71, 35-9, 1994 Ref Id 365566	Sample size See Cochrane SR Cheng 2015 Characteristics See Cochrane SR Cheng 2015 Inclusion criteria See Cochrane SR Cheng 2015 Exclusion criteria See Cochrane SR Cheng 2015	Interventions See Cochrane SR Cheng 2015	Details See Cochrane SR Cheng 2015	Results See Cochrane SR Cheng 2015	Limitations See Cochrane SR Cheng 2015 Other information See Cochrane SR Cheng 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Ireland Study type RCT Aim of the study Study dates Source of funding					
Full citation Konstan,M.W., Byard,P.J., Hoppel,C.L., Davis,P.B., Effect of high-dose ibuprofen in patients with cystic fibrosis, New England Journal of Medicine, 332, 848-854, 1995 Ref Id 233726 Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Lands 2016 Characteristics See Cochrane SR Lands 2016 Inclusion criteria See Cochrane SR Lands 2016 Exclusion criteria See Cochrane SR Lands 2016	Interventions See Cochrane SR Lands 2016	Details See Cochrane SR Lands 2016	Results See Cochrane SR Lands 2016	Limitations See Cochrane SR Lands 2016 Other information None.
Full citation	Sample size N: 224	Interventions GROUP 1: placebo	Details	Results	Limitations

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lai, H. C., FitzSimmons, S. C., Allen, D. B., Kosorok, M. R., Rosenstein, B. J., Campbell, P. W., Farrell, P. M., Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis, New England Journal of Medicine, 342, 851-9, 2000 Ref Id 329828 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study To evaluate the long-term growth of children with cystic fibrosis who had participated in a multicenter clinical trial (Eigen 1995) of treatment with	Characteristics Age range: 6 to 14 years GROUP 1: placebo: N: 73, Gender split: M: 35/ F: 3 GROUP 2: 1 mg Prednisone/kg: N: 75, Gender split: M: 46/ F: 29 GROUP 3: 2 mg Prednisone/kg: N: 76, Gender split: M: 29/ F: 31 Inclusion criteria Children who participated in the prednisone trial (Eigen 1995) Exclusion criteria Not reported	GROUP 2: 1 mg Prednisone/kg GROUP 3: 2 mg Prednisone/kg	Retrospective cohort study (10 years follow up of a Double-blind multicentre RCT - Eigen 1995)	Absolute height at 18 Years of Age - mean (SD); cm Male GROUP 1: placebo - N:21, 174.6 (6.8) GROUP 2: 1 mg Prednisone/kg -N:34, 170.7(7.6) GROUP 3: 2 mg Prednisone/kg -N:31, 170.5(6.6) Female GROUP 1: placebo - N:23, 160.3(6.9) GROUP 2: 1 mg Prednisone/kg - N:23, 159.3 (4.9) GROUP 3: 2 mg Prednisone/kg - N:20, 159.8(6.7) Absolute weight at 18 Years of Age - mean (SD); kg Male GROUP 1: placebo - N:21, 63.7(9.3) GROUP 2: 1 mg Prednisone/kg - N:34, 59.1(7.9) GROUP 3: 2 mg Prednisone/kg - N:31, 57.0(9.4) Female GROUP 1: placebo - N:23, 51.9(7.2)	The quality assessment was conducted using the NOS scale for observational studies: Selection: unclear risk (the participants were selected from a previous RCT. Although it can be argued randomisation was kept, it is not possible to determine whether participants received other treatments after the original trial was finished) Comparability: low risk of bias (The study does control for important factors such as lung disease) Outcome: high risk of bias (loss to follow-up in > 20%) Other information The study showed that growth slowed down to such an extent that it reduced the final height of 4 cm in prepubertal males, but not in females. This was a retrospective cohort study (10 years follow up of a RCT). There is some likelihood for attrition bias. The Authors identifi ed children who participated in the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
steroids (alternate day treatment with oral prednisone) from 1986 through 1991. Study dates 2000 Source of funding Supported by a postdoctoral research fellowship from the Cystic Fibrosis Foundation (to Dr. Lai) and a grant from the National Institutes of Health (2R01 DK34108).				GROUP 2: 1 mg Prednisone/kg - N:23, 49.6(7.6) GROUP 3: 2 mg Prednisone/kg - N:20, 53.6(10.1) Growth throughout the 10-Year Study Period (height and weight Z scores - p-value only) Height male: P=0.03 ("the z scores for height remained significantly lower in the two prednisone groups than in the placebo group after 10 years of follow-up" - P854). female: P=0.26 ("The z scores for height in girls treated with prednisone [...] were no significantly lower than those of girls who received placebo p855) Weight male: P=0.04 ("z scores for weight in boys treated with high-dose prednisone were significantly lower than those in boys who received placebo P855) female: P=0.84("no significant differences among the three groups	prednisone trial (Eigen 1995) and obtained data on their growth from the U.S. Cystic Fibrosis Foundation Patient Registry in Bethesda. Of the 285 children enrolled, 42 were Canadian; data on these patients therefore were not reported to the U.S. registry. Of the remaining 243 children, 19 could not be correctly identified from the registry.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				were found with regard to z scores for weight for the period after prednisone therapy was discontinued P855)	
Full citation Lands,L.C., Milner,R., Cantin,A.M., Manson,D., Corey,M., High-Dose Ibuprofen in Cystic Fibrosis: Canadian Safety and Effectiveness Trial, Journal of Pediatrics, 151, 249-254, 2007 Ref Id 237873 Country/ies where the study was carried out Canada Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Lands 2016 Characteristics See Cochrane SR Lands 2016 Inclusion criteria Exclusion criteria	Interventions See Cochrane SR Lands 2016	Details See Cochrane SR Lands 2016	Results See Cochrane SR Lands 2016	Limitations See Cochrane SR Lands 2016 Other information None.
Full citation Robinson, P., Schechter, M. S., Sly, P. D., Winfield, K., Smith, J.,	Sample size N: 63 Mean age (SD): 16 (10.5) years	Interventions 500 mg oral clarithromycin twice daily for 5 months (with a 1-month	Details Double blind crossover RCT.	Results Robinson 2012 Lung function (FEV1)	Limitations The quality assessment was conducted using the Cochrane risk of bias tool.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Brennan, S., Shinkai, M., Henke, M. O., Rubin, B. K., Clarithromycin therapy for patients with Cystic Fibrosis: A randomized controlled trial, Pediatric Pulmonology, 47, 551-557, 2012 Ref Id 361614 Country/ies where the study was carried out Australia Study type RCT Aim of the study The objective of this study was to evaluate the effect of clarithromycin on pulmonary function in adults and children with CF. Study dates 2012 (date of online publication) Source of funding This study was funded by research grants to BKR from the United States Cystic Fibrosis Foundation, Abbott	Characteristics Mean age (SD): 16 (10.5) years Gender split: 40 M/ 23 F Inclusion criteria proven diagnosis of CF defined as clinical symptoms presence of two recognized CF gene mutations and/or a positive sweat test as evidenced by sweat chloride level above 60 mmol/L by pilocarpine iontophoresis Exclusion criteria Subjects were excluded if they had: FEV1 < 30% predicted at enrollment, Mycobacterium in a sputum culture, a respiratory exacerbation requiring IV antibiotics in the 60 days before entering the protocol, or had used any investigational drug or device in the 60 days before entering the protocol. any significant (>30 ml) hemoptysis in the preceding year, requirement for oxygen therapy, or the presence of	wash-out) VERSUS placebo		Short-term FEV1 % predicted clarithromycin VERSUS placebo: N: 29; Mean (SD): 0.9 (9.8) VERSUS N: 23; Mean (SD): 1.4 (8.4) Short-term exacerbations per patient clarithromycin VERSUS placebo: n/N: 54/29 VERSUS n/N: 44/23 Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation Not reported Adverse effects (abdominal pain) Not reported Mortality Not reported	Random sequence generation: unclear risk of bias (Randomization table was generated by the Wake Forest University General Clinical Research Center Pharmacy) Allocation concealment: unclear risk of bias (No details given) Blinding: low risk of bias (Reported as double blinded) Incomplete outcome data: unclear risk of bias (ITT analysis performed, but relatively high number of withdrawal -10 out of 62 dropped out) Selective reporting: unclear risk of bias (All listed outcomes reported, but reporting was confined to those considered to be most important and findings which were not statistically significant were not reported) Other bias: low risk of bias (None identified) Other information 10 subjects withdrew from the study

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Laboratories, and the NIH (GCRC Grant to Wake Forest University).	any significant liver or renal disease Subjects allergic to or intolerant of macrolides, or who were taking medications that adversely interact with macrolide antibiotics (moxifloxacin, sildenafil, or pimozide) were not enrolled.				
Full citation Saiman, L., Anstead, M., Mayer-Hamblett, N., Lands, L. C., Kloster, M., Hocevar-Trnka, J., Goss, C. H., Rose, L. M., Burns, J. L., Marshall, B. C., Ratjen, F., A. Z. Azithromycin Study Group, Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial, JAMA, 303, 1707-15, 2010 Ref Id 331904	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Saiman, L., Marshall, B. C., Mayer-Hamblett, N., Burns, J. L., Quittner, A. L., Cibene, D. A., Coquillette, S., Fieberg, A. Y., Accurso, F. J., Campbell, P. W., 3rd, Macrolide Study, Group, Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial, JAMA, 290, 1749-56, 2003 Ref Id 331908	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA Study type RCT Aim of the study Study dates Source of funding					
Full citation Sordelli,D.O., Macri,C.N., Maillie,A.J., Cerquetti,M.C., A preliminary study on the effect of anti-inflammatory treatment in cystic fibrosis patients with Pseudomonas aeruginosa lung infection, International Journal of Immunopathology and Pharmacology, 7, 109-117, 1994 Ref Id 172282 Country/ies where the study was carried out Argentina Study type RCT	Sample size See Cochrane SR Lands 2016 Characteristics See Cochrane SR Lands 2016 Inclusion criteria See Cochrane SR Lands 2016 Exclusion criteria See Cochrane SR Lands 2016	Interventions See Cochrane SR Lands 2016	Details See Cochrane SR Lands 2016	Results See Cochrane SR Lands 2016	Limitations See Cochrane SR Lands 2016 Other information Included in NMA only.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Study dates Source of funding					
Full citation Southern,Kevin W., Barker,Pierre M., SolisMoya,Arturo, Patel,Latifa, Macrolide antibiotics for cystic fibrosis, Cochrane Database of Systematic Reviews, -, 2012 Ref Id 239262 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The SR aims to assess the optimal type, dose and duration of macrolide therapy by 1) testing the hypothesis that, in people with CF, macrolide antibiotics improve clinical status compared to placebo or another	Sample size 5 randomised control trials (RCTs) SR were included from this Cochrane: Clement 2006 Equi 2002 Saiman 2003 Saiman 2010 Wolter 2002 Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Clement 2006 N:82 young people with CF (40 in azithromycin group, 42 in placebo group. 35 in treatment group and 37 in placebo group completed trial) Age: 6-21 years, mean age 11.0 years, SD 3.3 years FEV1 >40% predicted Equi 2002 N: 41 children Age range: 8 - 18 years Saiman 2003	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Clement 2006 Azithromycin 250 mg tablet 3 times per week (>40 kg, 500 mg) versus placebo. Equi 2002 Azithromycin, 250 mg (500 mg if weight > 40 kg) once a day for 6 months versus placebo Saiman 2003 Azithromycin, 500 mg (250 mg if weight <40 kg) 3 days a week versus placebo Saiman 2010 Azithromycin (250 mg 3 times a week, increased to 500, if weight >36 kg) versus placebo; for 6 months Wolter 2002	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Clement 2006 Multicentre, double-blind, placebo-RCT Equi 2002 Randomised placebo controlled cross-over trial Saiman 2003 Multicentre placebo-RCT Saiman 2010 Multi-centre placebo-controlled parallel design Wolter 2002 Randomised placebo-controlled trial	Results Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Equi 2002 Lung function (% predicted FEV1 at 2 – 4 - 6 months) at 2 monthsN: 20; Mean (SD): 4.05 (7.45) VERSUS N: 21; Mean (SD): 0.76 (15.43) at 6 monthsN: 20; Mean (SD): 4.85 (9.71) VERSUS N: 21; Mean (SD): 2.35 (13.58) Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation (Free of pulmonary exacerbation) Hazard ratio azithromycin v placebo: not reported Adverse effects	Limitations Quality of the SR AMSTAR score: 10/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Clement 2006 Random sequence generation: low risk of bias ("Centralised secure randomisation department") Allocation concealment: low risk of bias (Centralised, study number assigned by interactive voice response system, study kits distributed by chief pharmacist in each centre) Blinding: low risk of bias (Identically packaged, all participants and investigators blinded) Incomplete outcome data: low risk of bias (A complete ITT analysis undertaken on primary outcome and pulmonary

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
antibiotic and 2) do not have unacceptable adverse effects. Study dates Searches up to 29 February 2012. Source of funding Not reported	N: 185 participants: Age, mean (SD) - years*: 20.2(7.9) in the Azithromycin group (n:87); 20.6(8.6) in the Placebo group (n:98) Eligibility: adults and children with CF (> 6 years) with chronic P. aeruginosa chest infection (> 1 year) and an FEV1 >30% predicted. Saiman 2010 N*: 263 Age, mean (SD) - years*: 10.7(3.25) in the Azithromycin group (n:131); 10.6(3.10) in the Placebo group (n:129) Eligibility: Young CF patients (6-18 years) without chronic P. aeruginosa airway infection (clear (2 or more cultures) for > 12 months) Wolter 2002 N:60 adult participants. Mean age 27.9 (SD, 6.5). The placebo group contained more men (20/30 versus 9/30), was taller, heavier and had better lung function (FEV1 mean (SD), 62.3 (24.8) versus 50.9 (18.)	Azithromycin, 250 mg once a day for 3 months versus placebo		Not reported Mortality Not reported Clement 2006 Lung function (% predicted FEV1 at 2 – 4 - 6 – 8 -10 -12 months) at 2 months N: 40; Mean (SD): 0.8 (16.6) VERSUS N: 42; Mean (SD): -1.3 (14.3) at 6 months N: 40; Mean (SD): 2.8 (18.3) VERSUS N: 42; Mean (SD): -3 (17.6) at 12 months N: 40; Mean (SD): -4.3 (17.9) VERSUS N: 42; Mean (SD): -1.5 (15.4) Quality of life measures actual data in each group were not reported Nutritional status (change in BMI z score at 12 months follow-up) N: 40; Mean (SD): 0.03 (0.40) VERSUS N: 42; Mean (SD): -0.12(0.44) Time to next pulmonary exacerbation (Free of pulmonary exacerbation at 6 and 12 months) Hazard ratio azithromycin v placebo 0.37 (95% CI 0.22 - 0.63).	exacerbation data. Some per protocol analysis on other outcomes) Selective reporting: unclear risk of bias (Some data at intermediate time points not reported -requested from authors, who kindly provided some IPD, although intermediate time points not available) Other bias: low risk of bias (None identified) Equi 2002 Random sequence generation: low risk of bias (Provided by Statistics Dept. at Pfizer, USA) Allocation concealment: low risk of bias (Hospital Pharmacy department, described in detail) Blinding: low risk of bias (All parties involved, identical packaging for intervention and placebo) Incomplete outcome data: low risk of bias (Complete ITT analysis undertaken on primary outcome. Not clear from paper whether primary outcome was a post hoc protocol change, but subsequent

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Exclusion criteria			Adverse effects Not reported Mortality Not reported Saiman 2003 Lung function (% predicted FEV1 at 1 – 3 - 6 months) at 1 months N: 87; Mean (SD): 4.01 (13.03) VERSUS N: 97; Mean (SD): 0.2 (9.1) at 3 months N: 87; Mean (SD): 2.33 (12.47) VERSUS N: 95; Mean (SD): 0.32 (11.99) at 6 months N: 84; Mean (SD): 4.44 (13.6) VERSUS N: 93; Mean (SD): -1.77 (10.66) Quality of life measures (Change in total quality of life score - CFQ-R)* physical factor N: 85; Mean (SD): 0.8 (9.9) VERSUS N: 92; Mean (SD): -1.9 (8.8) psychological factor N: 85; Mean (SD): 1.6 (12.1) VERSUS N: 92; Mean (SD): 1.2 (10.9) body image factor N: 85; Mean (SD): 3.1 (14.5) VERSUS N: 92; Mean (SD): 1.7 (14.8)	correspondence has confirmed that this was determined a priori) Selective reporting: low risk of bias (Not clear if primary outcome calculation (months 4 and 6 averaged for relative change) was an a priori decision) Other bias: low risk of bias (Adequate washout, authors have provided IPD) Saiman 2003 Random sequence generation: low risk of bias (By CF TDN Co-ordinating Centre. Randomisation included a valid allocation strategy to ensure equivalence between placebo and intervention with respect to weight, respiratory function and site of study) Allocation concealment: low risk of bias (Centralised secure randomisation system at the co-ordinating centre) Blinding: low risk of bias (All study personnel and participants) Incomplete outcome data: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Total N: 85; Mean (SD): 1.7 (7.5) VERSUS N: 92; Mean (SD): -0.1 (7.5) Nutritional (change in weight) Mean difference (SE): 0.7 (0.33) Time to next pulmonary exacerbation (Free of pulmonary exacerbation) Hazard ratio azithromycin v placebo 0.65 (95% CI 0.44 - 0.0.95) Adverse effects Not reported Mortality Not reported Saiman 2010 Lung function (% predicted FEV1 at 6 months) N: 125; Mean (SD): 5.4 (13.3) VERSUS N: 124; Mean (SD): 3.4 (12.4) Quality of life measures Not reported Nutritional status (change in weight, height, BMI)* actual data in each group were not reported Time to next pulmonary exacerbation (Free of pulmonary exacerbation)* Hazard ratio azithromycin v placebo 0.50 (95% CI 0.31- 0.79).	(Clear ITT analysis of primary outcome) Selective reporting: low risk of bias (Outcomes clearly reported. Subsequent subgroup analysis published separately) Other bias: low risk of bias (None identified) Saiman 2010 Random sequence generation: low risk of bias (University of South Florida generated assignments via secure centralized randomisation system) Allocation concealment: low risk of bias (Data co-ordinating centre distributed blinded study drug kits) Blinding: low risk of bias (Identically packaged tablets) Incomplete outcome data: low risk of bias (Modified ITT analysis (3 patients in placebo arm did not receive study drug and were removed) of primary outcome and most others) Selective reporting: low risk of bias (All outcomes reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse effects Not reported Mortality Not reported Wolter 2002 Lung function (% predicted FEV1 at 3 months) N: 22; Mean (SD): 2.95 (9.22) VERSUS N: 21; Mean (SD): -0.91(5.99) Quality of life measures (CRDQ) Not reported (Chronic Respiratory Disease Questionnaire, which is not validated in CF) Nutritional status Not reported Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality Not reported	Other bias: low risk of bias (Very clearly reported study) Wolter 2002 Random sequence generation: unclear risk of bias (Hospital pharmacy staff, exact method not stated - "randomised prior to commencement of study"). Allocation concealment: low risk of bias (By hospital pharmacy) Blinding: low risk of bias (Identical capsules and number, all parties blind) Incomplete outcome data: low risk of bias (ITT analysis performed on primary outcome, others reported per protocol) Selective reporting: low risk of bias (All outcomes reported) Other bias: unclear risk of bias (Baseline characteristics significantly different between interventions, see above "Participants") Other information None.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Wolter, J., Seeney, S., Bell, S., Bowler, S., Masel, P., McCormack, J., Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial, Thorax, 57, 212-6, 2002 Ref Id 332316 Country/ies where the study was carried out Australia Study type RCT Aim of the study Study dates Source of funding	Sample size See Cochrane SR Southern 2012 Characteristics See Cochrane SR Southern 2012 Inclusion criteria See Cochrane SR Southern 2012 Exclusion criteria See Cochrane SR Southern 2012	Interventions See Cochrane SR Southern 2012	Details See Cochrane SR Southern 2012	Results See Cochrane SR Southern 2012	Limitations See Cochrane SR Southern 2012 Other information Included in NMA only.
Full citation BalfourLynn, Ian M., Welch, Karen, Inhaled corticosteroids for cystic fibrosis, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 2016	Sample size 2 randomised control trials (RCTs) SR were included from this Cochrane: Balfour-Lynn 1997 (referred to as the UK trial in the Cochrane SR) Balfour-Lynn 2006 (referred to as the CF WISE 2006 trial in the Cochrane SR)	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Balfour-Lynn 1997 Fluticasone propionate 500 mcg	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Balfour-Lynn 1997 Randomised, double-blind, placebo-	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 * Balfour-Lynn 1997 See NMA data extraction	Limitations Quality of the SR AMSTAR score: 10/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Balfour-Lynn 1997

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 537371 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The SR aims to assess the effectiveness of regular use of inhaled corticosteroids (ICS) when compared to not receiving ICS, in the management of people with CF. in terms of: 1) lung function (including tests of lung function, bronchial hyperreactivity, exercise tolerance); 2) need for hospital admission or antibiotic treatment for respiratory exacerbations; 3) well-being of people with CF (in relation to nutritional status and quality of life); 4) survival rate;	Boeck 2007 (referred to a Belgian trial 2007 in the Cochrane SR) Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Balfour-Lynn 1997 36 participants, aged 16 years to 41 years, with established CF pulmonary disease Balfour-Lynn 2006 N: 171 (86 male) Participants aged over 6 years, diagnosed with CF and attending 18 paediatric and adult UK CF centers. Age range 6 - 53 years. Mean age 14 years in fluticasone group and 15.8 years in placebo group. Eligibility - age over 6 years, FEV1 ≥40% predicted. Participants excluded if had used oral corticosteroids within the previous 3 months or very high dose of ICS.	twice daily via a metered dose inhaler and spacer or matching placebo given for 2 years Balfour-Lynn 2006 Fluticasone propionate given at equivalent dose to ICS participant taking before trial entry or placebo via a volumatic spacer. de Boeck 2007 Fluticasone 500 mcg dry powder inhaler twice daily or lactose placebo dispensed in identical canister.	controlled, parallel trial. Balfour-Lynn 2006 Randomised, double-blind, placebo-controlled withdrawal trial of 8 months duration. de Boeck 2007 Randomised, double-blind, muticentre trial	Balfour-Lynn 2006 Lung function (%predicted FEV1 at 6 months) N: 84; Mean (SD): 76 (19) VERSUS N: 87; Mean (SD): 73 (18) Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation Inhaled corticosteroid VERSUS placebo - at 1 monthsn/N: 69/84 VERSUS n/N: 77/87 Inhaled corticosteroid VERSUS placebo - at 3 monthsn/N: 48/84 VERSUS n/N: 47/87 Inhaled corticosteroid VERSUS placebo - at 6 monthsn/N: 36/84 VERSUS n/N: 38/87 Adverse effects (changes in growth velocity - change in height (cm) at 8 months) N: 42; Mean (SD): 41 (2.2) VERSUS N: 38; Mean (SD): 35 (2.6) Mortality Not reported de Boeck 2007 Lung function	Random sequence generation (selection bias): Unclear risk (Described as randomised, but no further details given) Allocation concealment (selection bias) Unclear risk (Not reported) Blinding (performance bias and detection bias) - All outcomes: Low risk (Described as double-blind) Incomplete outcome data (attrition bias) - All outcomes: Low risk (More than 15% of participants were excluded, but reasons given and numbers equal across groups. At 24 months data on FEV1 were only available on 8 participants in the fluticasone group and 9 in the placebo group) Selective reporting (reporting bias) - Low risk (All outcomes reported) Balfour-Lynn 2006 Random sequence generation: low risk of bias (Randomisation by permuted blocks of 4) Allocation concealment: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and 5) harmful effects. Study dates Searches up to 03 September 2012. Source of funding Not Reported	de Boeck 2007 N: 29 Mean age: 8.2 years in the fluticasone group; 9.0 years in the placebo group* Eligibility: pre-pubertal children (20 from 1 centre and 9 from another centre) who were clinically stable (defined as at least 2 months after any hospital admission and 2 weeks after a respiratory exacerbation) with FEV1at least 60% predicted. Excluded if had intake of oral or inhaled steroids for more than 2 weeks within past 6 months or any intake of these drugs including intranasal steroids within last 4 weeks or a clinical diagnosis of aspergillosis or participating in another clinical trial Inclusion criteria See characteristics of included studies. Exclusion criteria See characteristics of included studies.			a) % predicted FEV1 at 6 months- N: 12; Mean (SD): 95 (13.84) VERSUS N: 15; Mean (SD): 91 (15.48) b) % predicted FEV1 at 6 months- N: 12; Mean (SD): 95 (13.84) VERSUS N: 15; Mean (SD): 97 (11.61) c) % predicted FEV1 at 12 months- N: 12; Mean (SD): 90 (20.76) VERSUS N: 15; Mean (SD): 88 (15.48) d) % predicted FEV1 at 12 months- N: 12; Mean (SD): 91 (17.3) VERSUS N: 15; Mean (SD): 92 (11.61) Quality of life measures Not reported Nutritional status Not reported Time to next pulmonary exacerbation Not reported Adverse effects (changes in growth velocity - change in height (cm) at 12 months) N: 12; Mean (SD): 3.96 (0.69) VERSUS N: 15; Mean (SD): 5.49 (1.47) Mortality Not reported	(Randomisation was carried out independently at the Clinical Trials & Evaluation Unit of Royal Brompton Hospital and allocation of individuals was carried out over the telephone to the trial centres) Blinding: low risk of bias (All trial personnel and participants were blinded to treatment -placebo). Incomplete outcome data: low risk of bias (Intention-to-treat analysis was based on all participants) Selective reporting: low risk of bias (All stated outcomes reported) Other bias: low risk of bias (No other potential source of bias identified) de Boeck 2007 Random sequence generation: low risk of bias (Stated that used random number sequence) Allocation concealment: unclear risk of bias (Not mentioned in text) Blinding: low risk of bias (Described as double-blind, but no details of who exactly was blinded.

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					Placebo dispensed in identical canister, so probably participant and clinician blinded) Incomplete outcome data: low risk of bias (Less than 15% of participants were excluded. Of the 20 initially included participants, 2 were excluded -1 discontinued treatment after 3 months and 1 did not keep follow-up appointments) Selective reporting: low risk of bias (All outcomes reported) Other bias: low risk of bias (No other potential source of bias identified) Other information Balfour-Lynn 2006 This study is a "withdrawal trial" in which participants who were already taking inhaled fluticasone were randomised to continue fluticasone or start placebo
Full citation Cheng, K., Ashby, D., Smyth, R. L., Oral steroids for long-term use in	Sample size 3 randomised control trials (RCTs) SR were included from this Cochrane: Auberch 1985	Interventions Where possible data were extracted from the Cochrane SR. The full text of the	Details Where possible data were extracted from the Cochrane SR. The full text of the	Results Where possible data were extracted from the Cochrane SR. The full text of the primary study	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual primary studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cystic fibrosis, Cochrane Database of Systematic Reviews, 12, CD000407, 2015 Ref Id 424435 Country/ies where the study was carried out Study type Cochrane SR Aim of the study This review aims to determine whether there is clear evidence that one anti-inflammatory treatment, oral corticosteroids, is beneficial in the treatment of lung disease in people with CF by assessing the following hypotheses for long-term anti-inflammatory use: reduce the number of days of intravenous antibiotics for respiratory exacerbations; reduce the need for hospital admission	Eigen 1995 Greally 1994 Characteristics Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Auberch 1985 N:45 (participants recruited) Age range: 1 - 12 years. Eligibility: CF diagnosed on clinical features and raised sweat electrolytes. Mild to moderate pulmonary disease. 24 assigned to placebo group and 21 to prednisone group. 11 participants did not complete study (7 placebo, 4 prednisone) - 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications. Eigen 1995 N: 285 (participants recruited) Age range 6 - 14 years Eligibility: CF diagnosed on clinical features and 2 raised sweat chloride (or sweat sodium) values; clinical stability	primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Auberch 1985 Prednisone 2 mg/kg (maximum 60 mg) on alternate days placebo Eigen 1995 Prednisone 2 mg/kg or prednisone 1 mg/kg on alternate days (maximum dose 60 mg) Placebo Participants who missed 30% or more of total prescribed study medication were labelled as non-compliant but still included in analysis. Greally 1994 Soluble prednisolone 2 mg/kg/ daily for 14 days and then 1 mg/kg/ day on alternate days for 10 weeks (maximum dose 40 mg) Identical inert placebo tablets	primary study was checked for accuracy and completeness. Auberch 1985 Double-blinded RCT Eigen 1995 Double-blinded multicentre (15 centres) RCT Greally 1994 Randomised. Double-blinded.	was checked for accuracy and completeness. Eigen 1995 Lung function (FEV1) actual data in each group were not reported Quality of life measures Not reported Nutritional status (weight) Not reported Time to next pulmonary exacerbation Not reported Adverse effects (a-cataracts; b-diabetes; c-grow retardation) a-cataracts Oral corticosteroids (1 mg prednisone) VERSUS placebon/N: 3/95 VERSUS n/N: 7/95 Oral corticosteroids (2 mg prednisone) VERSUS placebon/N: 11/95 VERSUS n/N: 7/95 b-diabetes Oral corticosteroids (1 mg prednisone) VERSUS placebon/N: 3/95 VERSUS n/N: 1/95 Oral corticosteroids (2 mg prednisone) VERSUS placebon/N: 6/95 VERSUS n/N: 1/95 c- grow retardation	The risk of bias assessment has been taken from the SR. Auberch 1985 Random sequence generation: unclear risk of bias (Described as randomised, but method not stated) Allocation concealment: unclear risk of bias (Unclear) Blinding: unclear risk of bias (Described as double-blind, but this might not have been possible since at the doses used, it would have been obvious which participants were in the treatment group) Incomplete outcome data: low risk of bias (11 participants did not complete study:7 placebo, 4 prednisone;- 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications) Eigen 1995 Random sequence generation: low risk of bias (Randomised within each centre by computer-generated random

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
for respiratory exacerbations; improve or prevent the decline in objective tests of lung function (forced expiratory volume in one second (FEV1); forced vital capacity (FVC); and forced expiratory flow 25-75% (FEF25-75)); improve exercise tolerance; improve nutritional status; are associated with adverse effects including changes in appearance including Cushingoid appearance, growth suppression, diabetes mellitus, cataracts, osteoporosis and opportunistic infection; improve quality of life; improve survival. Study dates Searches up to 15 May 2013. Source of funding	without hospitalisation for CF-related problems within 2 months of entry; serum IgG within 2 standard deviations of normal for centre or hypogammaglobulinaemia; reliable performance of lung function tests for at least 6 months prior to enrolling in trial; FEV1 > 60% predicted and FEV1/FVC ratio > 60% predicted. Exclusion criteria included previous treatment with oral, inhaled or nasal corticosteroids for more than 2 weeks within 6 months of entry or any form of corticosteroids in previous month, evidence of liver disease, treatment with non-steroidal anti-inflammatory treatment Greally 1994 N: 45 (participants recruited) -24 assigned to placebo group and 21 to prednisone group. Age range: 1 - 12 years. Eligibility: CF diagnosed on clinical features and raised sweat electrolytes. Mild to moderate pulmonary disease. Inclusion criteria			Oral corticosteroids (1 mg prednisone) VERSUS placebon/N: 24/95 VERSUS n/N: 11/95 Oral corticosteroids (2 mg prednisone) VERSUS placebon/N: 31/95 VERSUS n/N: 11/95 Mortality Not reported Auberch 1985 Lung function (%predicted FEV1 at 4 years)* N: 21; Mean (SD): 103 (not reported) VERSUS N: 24; Mean (SD): 83 (not reported) Quality of life measures Not reported Nutritional status (height and weight)* actual data in each group were not reported Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality (6 months follow up) n/N: 0/21 VERSUS n/N: 1/24 Greally 1994	number sequence in blocks of 6) Allocation concealment: unclear risk of bias (Unclear) Blinding: unclear risk of bias (Described as double-blind and same number of tablets given for each regimen, but true blinding might not have been possible since at the doses used, it would have been obvious from treatment effects which participants were in the treatment group) Incomplete outcome data: unclear risk of bias (Participants who missed 30% or more of total prescribed study medication were labelled as non-compliant but still included in analysis) Greally 1994 Random sequence generation: Unclear risk (Described as randomised, but method not stated) Allocation concealment: Unclear risk (Unclear) Blinding (performance bias and detection bias): All outcomes - Unclear risk (Described as

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
NHS North West Region R & D Programme, UK.	See characteristics of included studies. Exclusion criteria See characteristics of included studies.			Lung function (%predicted FEV1) (UP TO 2 WEEKS)N: 12; Mean (SD): 7.7 (7.97) VERSUS N: 12; Mean (SD): -1 (7.97) (UP TO 12 WEEKS)N: 12; Mean (SD): 6.3 (9.56) VERSUS N: 12; Mean (SD): -1.8 (9.56) Quality of life measures Not reported Nutritional status (absolute change in weight –kg) N: 13; Mean (SD): 0.35 (4.27) VERSUS N: 12; Mean (SD): 0.01 (2.31) Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality Not reported	double-blind and placebo and prednisolone tablets were identical, but true blinding might not have been possible since at the doses used, it would have been obvious which participants were in the treatment group) Incomplete outcome data (attrition bias): All outcomes - Low risk (No withdrawals) Other information Greally 1994 11 participants did not complete study (7 placebo, 4 prednisone) - 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications.
Full citation Lands, L. C., Stanojevic, S., Oral non-steroidal anti-inflammatory drug therapy for lung disease in cystic fibrosis, Cochrane Database of Systematic	Sample size 4 randomised control trials (RCTs) SR were included from this Cochrane: Konstan 1991 Konstan 1995 Lands 2007 Sordelli 1994 Characteristics	Interventions Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Konstan 1991	Details Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Konstan 1991	Results Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Additional data extracted is marked with a * Konstan 1991	Limitations Quality of the SR AMSTAR score: 11/11 Quality of the individual primary studies The risk of bias assessment has been taken from the SR. Konstan 1991

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Reviews, 4, CD001505, 2016 Ref Id 469625 Country/ies where the study was carried out Study type Cochrane SR Aim of the study The SR aims to determine the effectiveness of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) in preventing pulmonary deterioration and maintaining an optimal level of pulmonary function among those with CF. Study dates Searches up to 15 May 2013. Source of funding Internal sources (Institute of Child Health, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK	Where possible data were extracted from the Cochrane SR. The full text of the primary study was checked for accuracy and completeness. Konstan 1991 N: 19 children with CF Age range: 6-12 years. Eligibility: diagnosed clinically and by sweat test, aged 6-12 years. Eligible if FEV1 > 30% predicted for age, height and gender; judged to be clinically stable; no history of adverse effects with aspirin, ibuprofen or other NSAID; not taking 'interfering medication' (not defined). 13 (7 male) in treatment group and 6 (3 male) in placebo group. 1 female in placebo group dropped out on day 1 because of difficulty with venous access. Konstan 1995 N: 85 people with CF Age range: 5-39 years. Eligibility: people with CF, diagnosed clinically and by sweat test, not treated with intravenous antibiotics in preceding 2 months and with FEV1 at least 60%	3-month dose escalation study. Participants received 300 mg of drug orally and twice daily during the first month, and, depending on pharmacokinetic studies, 400 mg in the second month, and 600 mg in the third month. Control - placebo. Konstan 1995 Participants randomly assigned to receive high-dose oral ibuprofen twice daily for 4 years or placebo twice daily for 4 years. Dose 20-30 mg per kg of body weight, to a maximum of 1600 mg, determined by pharmacokinetic analyses. Lands 2007 All participants underwent a baseline pharmoacokinetic study (baseline every hour for 3 hours), employing 200 mg tablets (Upjohn-Pharmacia) at a	Double-blinded RCT, 3-month dose escalation study in children with CF. Konstan 1995 Double-blinded RCT Lands 2007 Multicentre double-blind RCT Sordelli 1994 RCT (no blinded)	Lung function (FEV1) actual data in each group were not reported Quality of life measures Not reported Nutritional status (absolute change in weight) Not reported Time to next pulmonary exacerbation Not reported Adverse effects (abdominal pain decrease)* n/N: 8/13 VERSUS n/N: 4/6 Mortality Not reported Konstan 1995 Lung function (% predicted FEV1) all ages N: 41; Mean (SD): -2.17 (3.65) VERSUS N: 43; Mean (SD): -3.6 (3.61) Under 13 years at randomisation N: 24; Mean (SD): -1.49 (3.77) VERSUS N: 25; Mean (SD): -4.2 (3.75) 13 years or over at randomisation N: 17; Mean (SD): -3.13 (3.22) VERSUS N: 18; Mean (SD): -2.77 (3.22)	Random sequence generation: low risk of bias (Adequate, randomisation was based upon a computer-generated randomisation sequence) Allocation concealment: low risk of bias (Adequate, the randomisation sequence was provided by the pharmaceutical company -Upjohn) Blinding: low risk of bias (Described as double blinded. The pharmaceutical company provided the clinics with identical-appearing placebo tablets) Incomplete outcome data: low risk of bias (Less than 15% of participants excluded (three participants) due to poor venous access, behavioural problems and difficulty in transport to follow up trial visits) Selective reporting: high risk of bias (Outcomes listed were reported, but the trial investigators monitored a large number of potential adverse effects of ibuprofen: reporting was confined to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
External sources (Tenovus, Scotland, UK)	predicted. 42 (26 male) were in the treatment group and 43 (15 male) in placebo group; age range 5-39 years. Exclusion criteria: systemic or inhaled corticosteroids used within two years of recruitment or inhaled sodium cromoglycate used within 6 months of recruitment. Lands 2007 N:142 children with CF Age range: 6-18 years. Eligibility: Inclusion criteria: FEV1 >60% predicted at time of entry into the trial, with no hospitalizations in the previous 2 months. Exclusion criteria: people who had taken systemic corticosteroids or non-steroidal anti-inflammatory agents for more than 1 month in the past year, had abnormal hepatic, renal, hematoologic disorders or coagulopathy, documented evidence of peptic ulcer disease(endoscopy) or allergic bronchopulmonary aspergillosis, or a history of hypersensitivity reactions to non-steroidal anti-inflammatory agents.	dose of 20 to 30 mg/kg to a maximum of 1600 mg. The number of assigned pills were then adjusted by the coordinating pharmacologist to provide a peak plasma concentration of 50 to 100 microg/ml for each participant in the study. Participants then were asked to take the prescribed number of pills (ibuprofen or placebo) twice daily Sordelli 1994 Participants were randomized to active treatment with piroxicam and 21 (11 male) to treatment with placebo. Piroxicam and placebo were taken by the participants in a single morning dose. Treatment was suspended during periods of hospitalization and reinstated after discharge.		Quality of life measures Not reported Nutritional status as (annual rate of change in % ideal body weight overall and by age) all ages N: 41; Mean (SD): 0.05 (1.97) VERSUS N: 43; Mean (SD): 0.94 (1.86) Under 13 years at randomisation N: 24; Mean (SD): -0.05 (2.01) VERSUS N: 25; Mean (SD): -1.5(2) 13 years or over at randomisation N: 17; Mean (SD): 0.19 (1.44) VERSUS N: 18; Mean (SD): -0.15 (1.44) Time to next pulmonary exacerbation Not reported Adverse effects (a- Increase in abdominal pain; b- Decrease in abdominal pain) a- Increase in abdominal pain n/N: 5/41 VERSUS n/N: 7/43 b- Decrease in abdominal pain N/N: 1/70 VERSUS n/N: 4/72 Mortality Not reported Lands 2007	those considered to be most important and findings which were not statistically significant were not reported) Other bias: unclear risk of bias (Reported adverse events) Konstan 1995 Random sequence generation: low risk of bias (Adequate, randomisation was carried out with permuted blocks of four participants each stratified by age (under 13 years, 13 to 18 years and 19 years or over) Allocation concealment: low risk of bias (Adequate, paper states that only the pharmacologist and pharmacist were privy to the allocation) Blinding: low risk of bias (Described as double blinded. The placebo tablets were identical in appearance to the ibuprofen tablets) Incomplete outcome data: low risk of bias (Analysis was based on intention-to-treat. A total of 28 participants withdrew from study, with

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Sordelli 1994 N: 41 people with CF Age range: 5 - 37 years Eligibility: people with CF, diagnosed by sweat test and clinically, and regularly attending the CF clinic at the Children's Hospital in Buenos Aires. Inclusion criteria See characteristics of included studies. Exclusion criteria See characteristics of included studies.	Participants for whom treatment was suspended for more than 30 days were removed from the trial		Lung function (FEV1) all ages N: 70; Mean (SD): -1.49 (4.77) VERSUS N: 72; Mean (SD): -2.69 (4.84) Under 13 years at randomisation N: 45; Mean (SD): -2.02 (4.63) VERSUS N: 53; Mean (SD): -2.44 (4.66) 13 years or over at randomisation N: 25; Mean (SD): -0.39 (5.05) VERSUS N: 19; Mean (SD): -3.59 (5.49) Quality of life measures Not reported Nutritional status (body mass index) Not reported Time to next pulmonary exacerbation Not reported Adverse effects (Increase in abdominal pain) n/N: 1/70 VERSUS n/N: 4/72 Mortality Not reported Sordelli 1994 Lung function (FEV1) See NMA data extraction Quality of life measures Not reported Nutritional status	similar numbers in both groups (15 in treatment group, 13 in placebo group). Selective reporting: high risk of bias (Outcomes listed were reported, but the trial investigators monitored a large number of potential adverse effects of ibuprofen: reporting was confined to those considered to be most important and findings which were not statistically significant were not reported) Other bias: unclear risk of bias (Intention-to-treat and completed treatment analysis are presented, intention-to-treat analysis was only used in the meta-analysis. Reported adverse events. Funded by the Cystic Fibrosis Foundation and the National Institutes of Health) Lands 2007 Random sequence generation: low risk of bias (Adequate, participants were allocated using a predefined block-randomisation schedule)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Not reported Time to next pulmonary exacerbation Not reported Adverse effects Not reported Mortality Not reported	Allocation concealment: low risk of bias (Adequate, a central pharmacy coded and shipped the tablets to the participating centers; the code was broken by the central pharmacy only on request from the Safety and Monitoring Committee) Blinding: low risk of bias (Described as double blinded. Paper states that participants, care-givers and study personnel were all blinded to treatment assignment) Incomplete outcome data: low risk of bias (Analysis was based on intention-to-treat. 18 participants -9 in each group- did not complete full 2 years of follow up, 11 due to adverse events -4 in treatment group, 7 in placebo group; details of these events in paper. Selective reporting: low risk of bias (Outcomes listed were reported) Other bias: unclear risk of bias (Reported adverse events. Funders did not have a role in the analysis or publication of results)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Sordelli 1994 Random sequence generation: unclear risk of bias (Authors confirmed randomised, but no details available regarding method yet) Allocation concealment: unclear risk of bias (No details given) Blinding: high risk of bias (Authors confirmed not blinded) Incomplete outcome data: unclear risk of bias (Insufficient information available to make judgement) Selective reporting: unclear risk of bias (Insufficient information available to make judgement) Other bias: unclear risk of bias (Insufficient information available to make judgement) Other information Konstan 1995 A total of 28 participants withdrew from study, with similar numbers in both groups (15 in treatment group, 13 in placebo group). Lands 2007

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					18 participants (9 in each group) did not complete full 2 years of follow up, 11 due to adverse events (4 in treatment group, 7 in placebo group).