G.9 Pulmonary infection - prophylaxis

Review question: What is the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with Staphylococcus aureus in people with CF?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Beardsmore,C.S., Thompson,J.R., Williams,A., McArdle,E.K., Gregory,G.A., Weaver,L.T., Simpson,H., Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment, Archives of Disease in Childhood, 71, 133-137, 1994 Ref Id 104558 Country/ies where the study was carried out Study type See Smyth 2014, Cochrane systematic review Aim of the study See Weaver 1994 Study dates - Source of funding -	Sample size See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information This study provides additional information for Weaver 1994.
Full citation Smyth, A. R., Walters, S., Prophylactic anti-staphylococcal antibiotics for cystic fibrosis, Cochrane Database of Systematic Reviews, 11, CD001912, 2014 Ref Id 367815 Country/ies where the study was carried out Study type	Sample size This review includes 4 trials. Characteristics Chatfield 1991 Infants with CF (diagnosed by	Interventions This review includes any oral antibiotic prophylactic intervention used continuously for a long period of time	Details All the studies included in the review are RCTs.	Results Data has been taken from the Cochrane SR where possible. Additional data has been extracted from	Limitations Limitations Quality of the systematic review AMSTAR score: 10 out of 11 Quality of the individual studies Data has been taken from the Cochrane SR where possible. Additional data has been extracted from studies if needed.

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cochrane systematic review Includes 4 RCTs: Chatfield 1991, Schlesinger 1984, Stutman 2002, Weaver 1994 NOTE: data has been extracted directly from the Cochrane SR where possible. Individual studies have been retrieved for completeness. Aim of the study This review aims to assess the effectiveness and safety of oral antibiotic prophylaxis to prevent the acquisition of S. Aureus versus no prophylaxis in people with CF. Study dates Searches up to 04.09.2014 Source of funding Not reported.	neonatal screening or clinically) N = 122 (2 withdrew, n = 120, prophylaxis = 54, 'as required' = 66) Mean age at enrollment: 18 weeks for prophylaxis & 22 weeks for 'as required'. Followed up to age three years. Data available at one, two & three years Stutman 2002 Children under 2 years 209 enrolled, and 119 completed the study (90 withdrew) n=68 in prophylaxis group and n=51 in placebo group	(> 1 year), compared with no prophylactic intervention to prevent the acquisition of S. aureus. Participants in both groups could receive intermittent courses of antibiotics if needed, on the basis of symptoms and organisms found in respiratory secretions. Interventions included in the individual studies: Chatfield 1991 Intervention: continuous oral Flucloxacillin Comparison: intermittent antibiotics 'as required'		studies if needed. Time to identification of the pathogen (S aureus) in sputum culture Not reported Number of positive pathogen cultures (S aureus) identified during study period, measured as number of children from whom S. aureus was isolated at least once by year of age (n/N) 1 year Chatfield 1991* Flucloxacillin group: 9/45 "as required" group: 19/51 Stutman 2002*	Chatfield 1991 Sequence generation: unclear risk (judgement: method not described, unclear) Allocation concealment: unclear risk (judgement: not described) Blinding - all outcomes: high risk (judgement: unbllinded, no placebo) Incomplete outcome data - all outcomes: unclear risk (judgement: ITT analysis not possible. Infants with meconium ileus not randomised and therefore excluded from analysis. One participant lost to follow up and one infant died) Selective outcome reporting: unclear risk (judgement: study reported outcomes up to three years of age. Only summary statistics have been presented in abstracts, and full paper describes the methodology, but does not present results by antibiotic groups) Other sources of bias: low risk (judgement: no other potential source of bias identified) Stutman 2002 Sequence generation: low risk (judgement: participant stratified by respiratory culture status. Permuted block design: blocks of 6, with 3 participants in each block randomised to cephalexin or placebo) Allocation concealment: low risk (judgement: treatment allocation known only to the study pharmacist. The pharmacist was responsible for

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Weaver 199 Infants with CF diagnosed by neonatal screening 42 participants enrolled, 4 withdrew (n = 38 prophylaxis = 18, 'as required' = 20) Similar mean ages at enrollment (7 weeks for prophylaxis, 5 weeks for 'as required') Followed up to age 2 years. Inclusion criteria See characteristics of included studies Exclusion criteria See characteristics of included studies	Stutman 2002 Intervention: continuous oral Cephalexin Comparison: placebo Weaver 1994 Intervention: continuous oral Flucloxacillin Comparison: intermittent antibiotics 'as required'		Cephalexin group: 11/75 "as required" group: 36/77 2 years Chatfield 1991* Flucloxacillin group: 10/51 "as required" group: 22/60 Stutman 2002* Cephalexin group: 19/87 "as required" group: 52/79 Weaver 1994* prophylaxis group: 3/18 "as required" group: 12/20 3 years Chatfield 1991* Flucloxacillin group: 12/54 "as required" group: 28/65 Stutman 2002* Cephalexin group: 25/77	increasing the dose of the prophylactic antibiotic as the children grew) Blinding - all outcomes: low risk (judgement: double-blinded, placebo-controlled) Incomplete outcome data - all outcomes: unclear risk (judgement: formal ITT analysis was not possible, however, analysis was performed for children completing treatment per protocol (n = 119) and those completing at least 1 year of the trial (n = 165)) Selective outcome reporting: low risk (judgement: measured and reported stated outcome variables yearly up to 6 years of age) Other sources of bias: low risk (judgement: no other potential source of bias identified) Weaver 1994 (Beardsman) Sequence generation: low risk (judgement: described as randomised in the published paper. Authors confirmed treatment was allocated on the basis of block randomisation and allocation was given by telephone from the co-ordinating centre) Allocation concealment: low risk (judgement: allocation of treatment was concealed from the local investigator until the participant was enrolled) Blinding - all outcomes: high risk (judgement: unblinded, no placebo)

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				"as required" group: 50/64 4 years Stutman 2002* Cephalexin group: 25/71 "as required" group: 47/56 5 years Stutman 2002* Cephalexin group: 20/58 "as required" group: 34/40 6 years Stutman 2002* Cephalexin group: 7/25 "as required" group: 14/18 Lung function, measured as FEV1 at 6 years (mean±SD) Stutman 2002* Cephalexin group:	Incomplete outcome data - all outcomes: unclear risk (judgement: ITT analysis was not possible) Selective outcome reporting: low risk (judgement: the study reported outcome variables at one and two years following study entry) Other sources of bias: low risk (judgement: no other potential source of bias identified) Other information

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1.1±0.25; N=68 "as required" group: 1.1±0.18; N=51 Lung function, measured by LCI Not reported Evidence of inflammation in CT scan (only for < 5 yrs) Crispin-Norman score at 1.3 years (mean±SD) Chatfield 1991* Flucloxacillin group: 5.71±1.84; N=48 "as required" group: 5.98±2.32; N=61 Time to next pulmonary exacerbation	

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Number of children requiring admission (annualised rates) Chatfield 1991* Flucloxacillin group: 10/40 "as required" group: 14/46 Stutman 2002* Cephalexin group: 5/68 "as required" group: 4/51 Weaver 1994* Flucloxacillin group: 7/18 "as required" group: 8/20 Pulmonary exacerbations (mean±SD) Stutman 2002** Cephalexin group: 61.8±48.6; N=68 "as required" group: 66.7±47.1; N=51	

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				QOL, measured by: o CFQoL (Gee 2000) o CFQ-R (Quittner 2009) Not reported Adherence to treatment (or patient preference) Not reported Adverse events, minor events Generalised rash (mean±SD) Stutman 2002* Cephalexin group: 0.6±1.7; N=68 "as required" group: 0.2±0.9; N=51 Nappy rash (mean±SD) Stutman 2002* Cephalexin group: 4±5.8; N=68	

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				"as required" group: 3.1±5.1; N=51 Increased stool frequency (mean±SD) Stutman 2002* Cephalexin group: 4.3±6.1; N=68 "as required" group: 4.1±6.9; N=51 Adverse events, major events Not reported Number of children from whom P. Aeruginosa isolated at least once 1 year Chatfield 1991* Flucloxacillin group: 6/44 "as required" group: 3/51 Stutman 2002*	

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Cephalexin group: 27/75 "as required" group: 24/77 2 years Chatfield 1991* Flucloxacillin group: 7/51 "as required" group: 8/60 Stutman 2002* Cephalexin group: 38/87 "as required" group: 40/79 Weaver 1994* prophylaxis group: 2/18 "as required" group: 6/20 3 years Chatfield 1991* Flucloxacillin group: 9/54 "as required" group: 14/66 Stutman 2002* Cephalexin group: 45/77	

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				"as required" group: 38/64 4 years Stutman 2002* Cephalexin group: 46/71 "as required" group: 33/56 5 years Stutman 2002* Cephalexin group: 41/58 "as required" group: 20/40 6 years Stutman 2002* Cephalexin group: 22/25 "as required" group: 12/18 Emergence of resistant organisms Not reported	
Full citation Stutman, H. R., Lieberman, J. M., Nussbaum, E., Marks, M. I., Antibiotic prophylaxis in	Sample size	Interventions	Details See Cochrane	Results	Limitations See Cochrane SR Smyth 2014 Other information

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
infants and young children with cystic fibrosis: a randomized controlled trial, Journal of Pediatrics, 140, 299-305, 2002 Ref Id 332098 Country/ies where the study was carried out UK Study type RCT Aim of the study To evaluate the effects of prophylactic treatment in infants born with CF. Study dates Source of funding Medical Research Council, the CF research trust, and the East Anglia health authority.	See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria See Cochrane SR Smyth 2014	See Cochrane SR Smyth 2014	SR Smyth 2014	See Cochrane SR Smyth 2014 The study also reports the following outcomes: Adherence to treatment: 85% vs 80% (statistical significance not reported)	None.
Full citation Weaver,L.T., Green,M.R., Nicholson,K., Mills,J., Heeley,M.E., Kuzemko,J.A., Austin,S., Gregory,G.A., Dux,A.E., Davis,J.A., Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period, Archives of Disease in Childhood, 70, 84-89, 1994 Ref Id 81026 Country/ies where the study was carried out USA Study type See Smyth 2014, Cochrane systematic review Aim of the study	Sample size See Cochrane SR Smyth 2014 Characteristics See Cochrane SR Smyth 2014 Inclusion criteria See Cochrane SR Smyth 2014 Exclusion criteria	Interventions See Cochrane SR Smyth 2014	Details See Cochrane SR Smyth 2014	Results See Cochrane SR Smyth 2014	Limitations See Cochrane SR Smyth 2014 Other information None.

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Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine if anti-SA prophylaxis is effective in preventing or delaying the infection with S. Aureus in infants with CF. Study dates 1987 to 1998 Source of funding The National Institute for Allergy and Infectious disease, the CF Trust foundation, and the Memorial Medical centre foundation.	See Cochrane SR Smyth 2014				

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