D.12 Pulmonary Infection prophylaxis

Item	Details
Key issue in the scope	Antimicrobial management in CF to: • Prevent bacterial colonisation • Treat acute pulmonary infection • Treat chronic pulmonary infection, including clinical exacerbations and colonisation
Review question in the scope	What is the effectiveness of antimicrobial treatment to: • Prevent bacterial colonisation • Treat acute pulmonary infection • Treat chronic pulmonary infection, including clinical exacerbations and colonisation

Item	Details
Review question for the protocol	What is the effectiveness of long-term antimicrobial prophylaxis to prevent pulmonary bacterial colonisation with Staphylococcus aureus in people with CF? (protocol 1)
Objective	The aim of this review is to compare the clinical and cost effectiveness of different antimicrobials given as long-term (more than 3 months) prophylaxis against bacterial colonisation to people with Cystic Fibrosis.
Language	English
Study design	• Systematic reviews • RCTs • Conference abstracts of RCTs (Only if RCTs unavailable and the quality assessment of abstracts will conducted based on the available information and if necessary the authors of abstracts will be contacted). Exclusions: Cross-over studies, as this study design will not allow evaluation of the effects of prophylaxis on long-term outcomes measures.
Population and directness	Infants, children, young people and adults with defined CF, diagnosed clinically and by sweat test or genetic testing. Population size and indirectness: • Studies where N<10 will not be included. • Studies with indirect populations will not be considered.
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • Infants and young children <3 years • Children 3-12 years • Young people and adults >12 years Sensitivity analysis: In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias. Sub-group analysis: In the presence of heterogeneity, the following subgroups will be analysed separately: • Duration of treatment

Intervention	Oral Antibiotics administration with any of the following, alone or in combination for long-term (more than 3 months) prophylaxis of infection, including:
	• Combination antibiotics
	  ○ Co-amoxiclav
	  ○ Co-trimoxazole
	• Penicillins
	  ○ Flucloxacillin
	• Beta-lactam antibiotics
	  ○ Cephalosporins
	  ○ Cefalexin
	  ○ Cefradine/cephradine
	• Tetracycline (only for over 12 years)
	• Macrolides
	  ○ Azithromycin

Comparison	• Placebo • No treatment • Antibiotic A vs antibiotic B

Item	Details

Outcomes	• Time to identification of the pathogen (S aureus) in sputum culture
	• Number of positive pathogen cultures (S aureus) identified during study period
	• Lung function, measured by:
	  ○ Lung clearance index (> 5 yrs)
	  ○ FEV1 (absolute values litres or % predicted or both) (> 7 yrs)
	  ○ Evidence of inflammation in CT scan (only for < 5 yrs)
	• Time to next pulmonary exacerbation
	• Quality of life (CF-QOL, CFQR)
	• Adherence to treatment
	• Adverse events
	  ○ Minor events:
	  ○ Major events which leads to discontinuation
	  ○ emergence of resistant organisms
	Note: change from baseline will be priorised over absolute values

Importance of outcomes	Critical outcomes for decision making: • Time to identification of the pathogen (S aureus) in sputum culture • Time to next pulmonary exacerbation
Setting	All settings in which NHS-commissioned health and social care is provided.
Search strategy	Sources to be searched: Medline, Medline In-Process, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase Limits (e.g. date, study design): Apply standard exclusions and English language filters. Limit to RCTs and systematic reviews in the first instance but download all study designs. See appendix E.9.1 for a full search strategy
Review strategy	Appraisal of methodological quality: • The methodological quality of each study will be assessed using an appropriate checklist as per NICE guidelines manual (The Cochrane Risk of Bias tool for RCTs). • The quality of the evidence will be assessed by GRADE for each outcome according to the process described in the NICE guidelines manual (2014). Synthesis of data: • Meta-analysis will be conducted where appropriate. • Final and change scores will be pooled and if any study reports both, change scores will be used in preference over final scores. • If studies only report p-values from parametric analyses, and 95% CIs cannot be calculated from other data provided, this information will be plotted in GRADE tables, but evidence may be downgraded. • If studies only report p-values from non-parametric analyses, this information will be plotted in GRADE tables without downgrading the evidence, as imprecision cannot be assessed for non-parametric analyses. Minimal important differences (MIDs): • Time to identification of the pathogen (S aureus) in sputum culture = GRADE default • Number of positive pathogen cultures (S aureus) identified during study period = GRADE default • Lung clearance index (> 5 yrs) = GRADE default • FEV1 = 5 percentage points

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	• Evidence of inflammation in CT scan (only for < 5 yrs) = GRADE default MIDTime to next pulmonary exacerbation = any difference • Quality of life: CF-QOL = 5; CFQ-R = 8.5 • Adherence to treatment = GRADE default • Minor adverse events = GRADE default • Major events which leads to discontinuation = any difference • Emergence of resistant organisms = GRADE default Default MIDs: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes. Review process: • This question will be prioritised for dual weeding • A list of excluded studies will be provided following weeding. • Evidence tables and an evidence profile will be used to summarise the evidence.
Equalities	• Psychological and behavioural issues are more likely in people with a lower socioeconomic status • Gender- outcomes are worse for women although there is no evidence that this is a consequence of difference in care • Geographical issues – care is given through specialist centres and this may be a problem if a person with CF is living in an isolated location.
Notes/additional information	None.