D.14 Pulmonary Infection - Antimicrobial agents for chronic pulmonary infection

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
Review question for the protocol	What is the effectiveness of antimicrobial regimens in suppressing chronic pulmonary infection in children and adults with CF with any of the following pathogens: • *Pseudomonas aeruginosa* • *Burkholderia cepacia complex* • *Staphylococcus aureus* • *Aspergillus fumigatus*
Objective	The aim of this review is to determine the clinical and cost-effectiveness of treatment with antimicrobial regimens to suppress chronic pulmonary infection in people with cystic fibrosis. Regimens aimed at bacterial suppression can be continuous or intermittent For example, options for suppressive treatments for P aeruginosa include colistimethate sodium which is given continuously and tobramycin or aztreonam which are given month on, month off with or without a second antibiotic in the intercurrent months. Inhaled and intravenous antibiotics are used to supress pulmonary infection. In some parts of the UK it is practice to schedule additional intermittent 2 week IV antimicrobial therapy (e.g. every 3 months) to ensure cover where there may have been non-adherence to suppressive antimicrobial treatment at home. Although this practice may be protective for lung disease when young, there is a concern that long term side effects can develop by adulthood e.g. hearing loss or renal failure associated with tobramycin. This review also aims to examine the clinical and cost-effectiveness of scheduled intermittent IV antimicrobial therapy in addition to oral/nebulised chronic suppressive therapy.
Language	English
Study design	• Systematic reviews of RCTs • 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).
Population and directness	Children and adults with cystic fibrosis (diagnosed clinically and by sweat test or genetic testing) and chronic pulmonary infection without an exacerbation of their

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	pulmonary disease with one of the following specific pathogens identified in sputum/airway cultures: • *Pseudomonas aeruginosa* • *Burkholderia cepacia complex* • *Staphylococcus aureus* • *Aspergillus fumigatus* Population size and indirectness: • Studies where N<30 (N<15 for crossover trials) will not be included. • Studies with indirect populations will not be considered.
Stratified, subgroup and adjusted analyses	Stratified analyses: • Type of pathogen • Route of administration • Duration of treatment Sensitivity analysis: In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias. In the presence of heterogeneity, the following subgroups will be considered for subgroup analysis: • Patients known to be receiving treatment with immunomodulatory agents and/ or mucolytic agents • Patients with prior exposure to the treatment (prior vs naïve) Important confounders to be considered if comparative observational studies are included: • Concurrent treatment with immunomodulatory and/or mucolytic agents • Any other confounders noted in studies • Age is not considered to be an important confounder
Intervention	**For *Burkholderia cepacia* complex** • Ceftazidime* (inhaled, nebulised) • Cotrimoxazole (oral) • Meropenem* (inhaled, nebulised) • Imipenem (inhaled, nebulised) • Trimethoprim (oral) **For *Staphylococcus aureus*** • Flucloxacillin (oral) • Cotrimoxazole (oral) • Doxycycline (oral) • Cefradine (oral) **For *Pseudomonas aeruginosa*** • Colistimethate sodium* (dry powder for inhalation, nebulised) • Tobramycin (dry powder for inhalation, nebulised) • Aztreonam lysine* (inhaled, nebulised) • Azithromycin (oral, antibiotic-dose only) • Ciprofloxacin (oral) • Fosfomycin (inhaled)

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	For *Aspergillus fumigatus* • Itraconazole (oral) • Voriconazole (oral) • Amphotericin (inhaled, nebulised) • Posaconizole (oral)
Comparison	• Placebo • No treatment • The antibiotics listed in the interventions group (other than the one tested as intervention) • Different combinations of drugs
Outcomes	• Lung function: ○ FEV1 ○ CT Scans for under 5s • Time to next pulmonary exacerbation • Number of patients with at least 1 pulmonary exacerbation • Eradication of the specified organism from sputum/airway cultures • Nutritional status (BMI, weight/ height) • Quality of life (CF-QOL, CFQR) • Adverse events: ○ mild, that require transient discontinuation of treatment ○ severe, that require discontinuation of treatment • Emergence of resistant organisms/ antibiotic resistance Note: change from baseline will be priorised over absolute values
Importance of outcomes	Critical outcomes for decision making: • FEV1 • 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, CCTR, CDSR, DARE, HTA, 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. Supplementary search techniques: No supplementary search techniques were used. See appendix E.9.3 for full strategies
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

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	• Network meta-analysis will be conducted for chronic infection with each organism where there is sufficient evidence for an outcome (see separate protocol). • 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): • Eradication of the specified organism from sputum/airway cultures (complete eradication): any difference will be considered clinically significant • FEV1: 3 percentage points • CT Scans for under 5s: resolution of all inflammatory scans • Time to next exacerbation: any difference will be considered clinically significant • Nutritional status (BMI, weight/ height): GRADE default • Quality of life: CF-QOL = 5; CFQ-R = 4 • Adverse events: GRADE default • Serious adverse events leading to discontinuation of treatment: any difference will be considered clinically significant • Emergence of resistant organisms/ antibiotic resistance: 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. • This question will be prioritised for data extraction. • 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	Cystic fibrosis Trust, “ANTIBIOTIC TREATMENT FOR CYSTIC FIBROSIS”. Retrieved from: https://www.cysticfibrosis.org.uk/media/82010/CD_Antibiotic_treatment_for_CF_May_09.pdf Note in evidence tables (see corresponding NMA protocol): • Prior exposure to study drug • Baseline values (for FEV1) • Current treatment with mucolytic agents • Current treatment with immunomodulatory agents • Age