D.13 Pulmonary Infection - Antimicrobials for the treatment of acute pulmonary infection or those with an exacerbation

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 treatment for acute pulmonary infection or those with an exacerbation in children and adults with cystic fibrosis? (protocol 2)
Objective	The aim of this review is to compare the clinical and cost effectiveness of different antimicrobial regimens in achieving clinical resolution of acute pulmonary infection or exacerbation in children and adults with cystic fibrosis. In this evidence review, pulmonary exacerbation was defined in accordance with: • Fuchs definition (original form (4/16 symptoms leading to IV antibiotic treatment) or modified form (4/16 symptoms leading to any change in antibiotic therapy) • or

Item	Details
	• European CF Society Consensus definition: "need for additional antibiotic treatment as indicated by a recent change in at least 2 of 6 defined symptoms". Additionally, acute infection a person with cystic fibrosis who is found on routine microbiological investigation to have a significant respiratory pathogen (newly identified infection).
Language	English
Study design	• Systematic reviews • RCTs • Cross-over trials: only the first period of intervention prior to cross-over trials will be included. • 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 CF (diagnosed clinically and by sweat test or genetic testing) who present with clinical manifestations suggesting development of an acute pulmonary infection or those with an exacerbation and who are already known to have a positive sputum/airway culture for one of the following pathogens at entry to the trial: • *Staphylococcus aureus* • *Pseudomonas aeruginosa* • *Burkholderia cepacia complex* • *Haemophilus influenza* • *Nontuberculous mycobacteria (Mycobacterium avium complex and Mycobacterium abscessus)* • Children and adults with CF who present with clinical manifestations suggesting development of an acute pulmonary infection or those with an exacerbation without an identified pathogen at trial entry Population size and indirectness: • Studies where N< 20 will not be included. • Studies with indirect populations will not be considered.
Stratified, subgroup and adjusted analyses	Stratified analyses: • Type of pathogen 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: • Route of administration • Duration of treatment • Dose
Intervention	**For *Staphylococcus aureus*** • Flucloxacillin (oral or IV) • Cotrimoxazole (oral or IV) • Doxycycline (oral) (not for under 12's) • Cefradrine (oral) **For *Pseudomonas Aeruginosa*** (inhaled, IV, oral) • Ciprofloxacin (Cipro) (oral)

Item	Details
	• Aztreonam (inhaled or IV) • Ceftazidime IV • Meropenem IV • Piperacillin-Tazobactam IV • Fosfomycin IV • Ticarcillin-Clavulanate IV • Aztreonam (inhaled or IV) • Chloramphenicol (oral) • Sequencing antibiotics- Ciprofloxacin (oral) then either Colistin or Tobramycin (inhaled) **(first infection only)** **For *Burkholderia Cepacia complex*** (oral or IV) • Cotrimoxazole • Meropenem (IV or inhaled) • Ceftazidime (IV or inhaled) • Temocillicin • Imipenem • Trimethoprim • Tobramycin **For *Haemophilus influenzae*** (IV) • Co-amoxiclav (oral or IV) • Cefuroxime (IV) • Cefaclor • Cefixime • Doxycycline (>12 years) • Macrolide (clarithromycin/azithromycin) **Nontuberculous mycobacteria (*Mycobacterium avium complex*)** • Clarithromycin (oral) • Azithromycin (oral) • Rifampicin (oral) • Ethambutol (oral) • Amikacin (inhaled and potentially IV) **Nontuberculous mycobacteria (*Mycobacterium abscessus*)** • Cefoxitin (IV) • Clarithromycin (IV) • Amikacin (IV and inhaled) • Meropenem (IV and inhaled) • Tigecycline • Co-trimoxazole (oral) • Moxifloxacin (oral) • Ciprofloxain (oral) • Doxycycline/minocycline (tetratcyclines) (oral) • Linezolid (oral) • Clofazimine (oral) No identified pathogen at entry level

Item	Details
	• Any of the antibiotics listed above
Comparison	• Antibiotic A vs. antibiotic B • Combinations of antibiotics • Single vs combination
Outcomes	**Pulmonary exacerbation:** • Lung function: ○ Lung Clearance Index (LCI) ○ FEV1 ○ CT Scans for under 5s • Eradication of specific pathogen • Resolution of infection/exacerbation or measure of treatment failure (e.g. need for additional antibiotics) • Duration of the acute episode • Quality of life (CF-QOL, CFQR) • Mortality • Adverse events ○ mild, that require transient discontinuation of treatment ○ severe, that require discontinuation of treatment **For acute infection:** • Lung function: ○ Lung Clearance Index (LCI) ○ FEV1 ○ CT Scans for under 5s • Eradication of specific pathogen • Time to next pulmonary exacerbation • Resolution of infection/exacerbation or measure of treatment failure (e.g. need for additional antibiotics) • Quality of life (CF-QOL, CFQR) • Adverse events ○ mild, that require transient discontinuation of treatment ○ severe, that require discontinuation of treatment Note: change from baseline will be priorised over absolute values
Importance of outcomes	Critical outcomes for decision making: • Eradication of specific pathogen • Lung function: ○ Lung Clearance Index (LCI) ○ FEV1 ○ CT Scans for under 5s
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. Supplementary search techniques: No supplementary search techniques will be used. See appendix E.9.2 for full search strategy
Review strategy	Appraisal of methodological quality:

Item	Details
	• 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): • Eradication of the pathogen: any change will be considered clinically significant • Lung function: ○ LCI = GRADE default ○ FEV1 = deterioration of 3 percentage points ○ CT Scans for under 5s = resolution of all inflammatory scans • Resolution of acute infection or measure of treatment failure (e.g. need for additional antibiotics) = any change • Quality of life: CF-QOL = 5; CFQ-R = 8.5 • Adverse events: GRADE default • Serious adverse events leading to discontinuation of treatment: any change will be considered clinically significant 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	http://www.cff.org/UploadedFiles/treatments/CFCareGuidelines/Respiratory/CF-Care-Guidelines-Pulmonary-Exacerbations.pdf Topic group agree that if the definition of infection given in the paper is not relevant evidence will be downgraded for indirectness TG agreed that we will use the definition of an acute exacerbation given in the paper and downgrade by 1 or 2 if it does not match accepted definitions (see EMA 2002)

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	1) Fuchs definition (original form (4/16 symptoms leading to IV antibiotic treatment) or modified form (4/16 symptoms leading to any change in antibiotic therapy) or 2) European CF Society Consensus definition: “need for additional antibiotic treatment as indicated by a recent change in at least 2 of six defined symptoms”.