Adult Cystic Fibrosis Treatment of Infection Guideline

Choice of antibiotics in cystic fibrosis is based on several factors including organism sensitivity, history of adverse reactions or allergy and severity of symptoms. In most cases, at least two antibiotics are prescribed together in order to limit the emergence of super-infection with resistant strains or pathogens which may be present in sputum but not consistently present on culture.

Antibiotic regimens should be based on sputum sensitivity results, however a response is often observed despite *in vitro* resistance. Synergy testing may be useful to guide antimicrobial choice where multi-resistant organisms are cultured. Treatment regimens should be tailored to maximise individual patient needs in order to maximise adherence and minimise adverse effects. Doses stated are based on non pregnant adult patients with normal renal and hepatic function.

Most patients should be prescribed at least two antibacterial agents in combination. These may be given orally, intravenously or in combination. The oral route is usually acceptable where available and absorption not a concern. Several of the agents are only available parenterally and patients will normally be trained to self-administer, often using a Totally Implantable Intravenous Access Device (TIVAD). In patients colonised by multiple pathogens often a third (or more) antibiotic may be required. Specialist advice is required in complex cases via the NHS Tayside Complex Pulmonary Infection MDT (CPIT) which includes respiratory, ID and specialist pharmacy representation.

This is a guideline only and individual patient factors should be considered when selecting treatment, including:

- Interactions should be checked, especially in post-transplant patients who will be taking immunosuppressant drugs
- Low body weight patients, under 50kg may require a dose reduction
- Doses may need to be reduced in renal impairment
- History of allergic reactions or intolerances is more common in the CF population

Treatment is usually initiated based on assessment of lung function including spirometry results, chest radiograph, signs of infection, respiratory symptoms and changes in volume or colour of sputum. Currently, courses are generally given for 14 days but shorter courses of 7 to 10 days maybe given on advice of CF team for specific patients. Response to treatment should be assessed at the end of the course or earlier if required (e.g. adverse effect or worsening symptoms). A third week of treatment may be considered by the CF Team if there has been a partial response. Poor response requires review of treatment.

In NHS Tayside, adult patients are supplied with course of IV antibiotics from hospital pharmacy. Oral and nebulised antibiotic treatment for longer term courses may be commenced in hospital but further may be requested from their General Practitioner.

Local practice is to withhold nebulised and oral prophylactic antibiotics during a course of intravenous antibiotics to avoid toxicity, with the exception of azithromycin which should continue, unless there are any specific interactions.

Adapted with kind permission from NHS Lothian Guidance 2020

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1. Common CF Infections

Two agents should be used guided by patient's individual tolerances and susceptibility results. See notes above for further advice.

Colonising organisms	Recommended therapy	Notes
Haemophilus influenzae* and *Staphylococcus aureus Mild symptoms	**Co-amoxiclav** 625mg every 8 hours orally + **Amoxicillin** 500mg every 8 hours orally *+/-* **Ciprofloxacin** 750mg every 12 hours orally (see notes) *Penicillin allergy:* **Doxycycline** 100mg every 12 hours orally *or* **Clarithromycin** 500mg every 12 hours orally *+/-* **Ciprofloxacin** 750mg every 12 hours orally (see notes)	Co-amoxiclav covers both *H. influenzae* and *S. aureus* (MSSA). The increased dose of oral co-amoxiclav (achieved by additional amoxicillin) is required for treatment of *H. influenzae* Ciprofloxacin covers *H. influenzae* and *P. aeruginosa* which is useful where *P. aeruginosa* is grown intermittently and to reduce the risk of *P. aeruginosa* super-infection which can be unmasked by treatment with a single anti-staphylococcal agent. For MRSA infections seek advice from CPIT/ID/Microbiology Ciprofloxacin may not be required in mild exacerbations where there is little or no risk or previous history of *P. aeruginosa* infection. Ciprofloxacin use with caution in epilepsy and adolescents, can cause QT prolongation and always check for interactions. See fluoroquinolone warnings document. Clarithromycin - can cause QT prolongation and always check for interactions Doxycycline can cause photosensitivity. Ciprofloxacin/doxycycline – iron, calcium, magnesium and antacids can reduce absorption very significantly – time doses appropriately
Haemophilus influenzae* and *Staphylococcus aureus Moderate to severe symptoms Or Failure of first line therapy	**Co-amoxiclav** 1.2g every 8 hours IV *Plus* **Ciprofloxacin** 750mg every 12 hours orally If ciprofloxacin already used in first line therapy: Piperacillin / Tazobactam 4.5g 6 hours IV monotherapy. Given as 30 minute infusion as inpatient; IV bolus for home administration	

2. *Pseudomonas aeruginosa*

Two agents should be used guided by patient's individual tolerances and susceptibility results. See notes above for further advice.

2a. *Pseudomonas aeruginosa* eradication		
	Recommended therapy	**Notes**
1st choice	**Ciprofloxacin** 750mg every 12 hours orally *Plus* **Tobramycin** 300mg every 12 hours nebulised for 4 weeks	Recheck sputum at 6 weeks. Stop treatment if negative. Continue for 3 months if remains positive. 3 negative samples required, over 6 months to confirm successful eradication. Test dose of nebulised antibiotics required before commencing treatment. After two failed attempts at eradication, give two weeks of suitable intravenous antimicrobial therapy followed by a further course of eradication therapy including nebulised tobramycin. After multiple failures, patient is likely to be colonised. See table 3c for long term suppressive therapy. Ciprofloxacin use with caution in epilepsy and adolescents, can cause QT prolongation and always check for interactions. See fluoroquinolone warnings document.
2nd choice	**Ciprofloxacin** 750mg every 12 hours orally *Plus* **Colistimethate sodium** 2MU every 12 hours nebulised for 6 weeks Continue for a further 6 weeks if sputum remains positive.	
Failure of eradication or current exacerbation	Intravenous antibiotics for 2 weeks *Then* **Ciprofloxacin** 750mg every 12 hours orally *Plus* **Tobramycin** 300mg every 12 hours nebulised for 4 weeks	

2b. *Pseudomonas aeruginosa* exacerbation		
	Recommended therapy	**Notes**
Oral treatment	**Co-amoxiclav** 625mg every 8 hours orally + **Amoxicillin** 500mg every 8 hours orally *Plus* **Ciprofloxacin** 750mg every 12hours orally	Co-amoxiclav covers *Haemophilus influenzae* and *Staphylococcus aureus* which will also be present. Ciprofloxacin use with caution in epilepsy and adolescents, can cause QT prolongation and always check for interactions. See fluoroquinolone warnings document.
Intravenous treatment	**Ceftazidime** 2g every 8 hours (max 3g every 8 hours – use higher dose if >60kg) *or* **Piperacillin/tazobactam** 4.5g every 6 hours. Given as 30min IV infusion as in-patient; IV bolus for home patients *or* **Meropenem** 2g every 8 hours IV (<40kg 1.5g every 8 hours) *or* **Aztreonam** 2g every 6 hours IV *Plus either* **Tobramycin** [see guideline] IV or **Colistimethate sodium** 2MU tds IV (<60kg reduce dose to 1.5MU tds)	Combination of beta-lactam with tobramycin or colistimethate sodium is synergistic. Initial tobramycin dose should be based on the current Tobramycin Dosing Guideline for Adult CF or the dosage regimen that was previously identified as suitable for the patient. Determination of serum concentrations is required - see guideline for details. Avoid prolonged or regular courses of tobramycin due to risk of accumulation in the inner ear. Check if patient has had genetic testing for mitochondrial mutation associated with increased risk of ototoxicity. If confirmed patient has mutation avoid aminoglycoside if possible. If patient has not had test request aminoglycoside genetic testing (m.1555A>G) on ICE. Consider prescribing colistimethate sodium on alternate courses where regular IV tobramycin is required in order to limit ototoxicity if sensitivities allow. Note colistimethate sodium is also renally toxic and neurotoxic (usually dose related). There is some evidence that a combination of ceftazidime + meropenem are effective where both tobramycin and colistimethate sodium are not suitable e.g. due to renal toxicity.
Multiple allergies or multi-resistant PA	Discuss at CPIT MDT with ID or Microbiology input – synergy testing may be indicated	

2c. *Pseudomonas aeruginosa* chronic infection		
	Recommended therapy	**Notes**
Step 1	**Azithromycin** 500mg THREE times weekly orally (250mg THREE times weekly if <40kg)	Check LFTs/ECG before starting treatment and every 6 months. Avoid single macrolide in presence of non-tuberculous mycobacteria to reduce the risk of resistance.
Step 2	**Colistimethate sodium** every 12 hours nebulised or inhaled *or* **Tobramycin** every 12 hours nebulised or inhaled alternate months	Test dose of inhaled antibiotics is required before commencing treatment. Withhold nebulised antibiotic during courses of intravenous antibiotics to limit risk of cumulative toxicity. Both colistimethate sodium and tobramycin are available as dry powder inhalers and nebulised treatment. Dry powder inhalers are generally more convenient for patients and do not require equipment and cleaning.
Step 3	**Aztreonam** 75mg every 8 hours nebulised alternate months *or* **Levofloxacin** 240mg every 12 hours nebulised alternate months	Nebulised aztreonam or levofloxacin can be used when nebulised/inhaled colistimethate sodium and nebulised/inhaled tobramycin are not tolerated or not providing satisfactory therapeutic benefit as per SMC advice. For levofloxacin nebules consideration should be given to fluoroquinolone warnings

3. Other gram-negative infections

Two agents should be used guided by patient's individual tolerances and susceptibility results. See notes above for further advice.
When *Pseuodomonas* is also present 3 agents may be required to cover multiple pathogens. Seek advice from CPIT +ID/Microbiology as required.

3a. *Burkholderia cepacia complex*

	Recommended therapy	Notes
Oral treatment	**Co-trimoxazole** 960mg every 12 hours orally *plus* **Minocycline** 100mg every 12 hours orally *or* **Chloramphenicol*** 500mg every 6 hours orally	*B. cepacia* species is inherently resistant to most anti-pseudomonal penicillins, aminoglycosides and colistimethate sodium. Typing required – samples sent to reference lab. Synergy should be checked once a year. *Oral chloramphenicol is **expensive** and requires monitoring of FBC for bone marrow toxicity. Irreversible aplastic anaemia reported. Prolonged or repeated courses should be avoided. Follow NHS Scotland guidance
Intravenous treatment	**Ceftazidime** 2g every 8 hours (max 3g every 8 hours) *or* **Piperacillin/tazobactam** 4.5g every 6 hours. Given as 30min IV infusion as in-patient; IV bolus for home patients *or* **Meropenem** 2g every 8 hours IV (<40kg 1.5g every 8 hours) *or* **Temocillin** 2g every 8 hours IV *plus* another agent (see notes and seek advice if required)	Regimen should include at least 2 active agents to cover both *P. aeruginosa* and *B. cepacia* (3 or more agents may be required to cover multiple pathogens). This usually includes a combination of a beta-lactam plus tobramycin or colistimethate sodium and one other agent (which can be given orally). Minocycline - iron, calcium, magnesium and antacids can reduce absorption very significantly – time doses appropriately .

4b. *Stenotrophomonas maltophilia*		
	Recommended therapy	**Notes**
Oral treatment	**Co-trimoxazole** 1440mg every 12 hours orally *or* **Minocycline** 100mg every 12 hours orally	*S. maltophilia* is inherently resistant to most anti-pseudomonal penicillins, aminoglycosides and colistimethate sodium. Synergy should be checked once a year. Combinations of ceftazidime + tobramycin or ciprofloxacin or piperacillin/tazobactam + co-trimoxazole may be active. Minocycline - iron, calcium, magnesium and antacids can reduce absorption very significantly – time doses appropriately Patients will usually require antimicrobials to cover additional organisms. There is little experience with 2nd line agents for *S. maltophilia* but they may be useful to consider if the oral route is not available, where other agents are not tolerated or IV therapy is justified e.g. severe symptoms and/or hospitalised.
Intravenous treatment	**Co-trimoxazole** 1440mg every 12 hours IV infusion For other IV options discuss at CPIT with ID/Microbiology input	

4c. Achromobacter (Alcaligenes) xylosoxidans		
	Recommended therapy	**Notes**
Oral treatment	**Co-trimoxazole** 960mg every 12 hours orally *and* **Minocycline** 100mg every 12 hours orally *or* ***Chloramphenicol** 500mg every 6 hours orally	*A. xylosoxidans* is inherently resistant to most anti-pseudomonal penicillins, cephalosporins, aminoglycosides and quinolones. Synergy should be checked once a year. Minocycline - iron, calcium, magnesium and antacids can reduce absorption very significantly – time doses appropriately *Oral chloramphenicol is expensive and requires monitoring of FBC for bone marrow toxicity. Irreversible aplastic anaemia reported. Prolonged or repeated courses should be avoided. Follow NHS Scotland Guidance
Intravenous treatment	For IV options discuss at CPIT with ID/Microbiology input	

4. Fungal infections

4a. Oral candidiasis		
Likely organisms	**Recommended therapy**	**Notes**
Candida albicans	**As per NHS Tayside Guidance** **Always check fluconazole interactions with other medicines especially CF modulators e.g. kaftrio/ivacafator**	Commonly occurs with systemic steroids and/or broad spectrum antibiotics. Oral fluconazole will also cover vaginal candida. Persistent or recurrent candidiasis may respond to regular antifungal treatment weekly for 4 weeks. Treatment failure or recurrence should be investigated further by confirmation of organism and sensitivities.
4b. ABPA (*Aspergillus sp.*)		
Presence in sputum alone does not require treatment.	**Prednisolone** 0.5mg/kg every 24 hours orally for 1-2 weeks. Taper dose over 2-3 months based on clinical progress. Poor response or as steroid-sparing agent: Add **Itraconazole liquid** orally 3-6 months Follow NHS Tayside guidance for dosing and monitoring	Consider treatment where diagnostic criteria met: • acute clinical deterioration; • total IgE >500-1000 IU/ml; precipitins or IgE antibody to *A.fumigatus*; • new abnormalities on chest X-ray or CT not cleared by standard antibiotics or physiotherapy. • Raised eosinophils
4c. Chronic or Invasive pulmonary aspergillosis		
Seek expert advice from CPIT with ID/Microbiology input. Local guidance available here		

4. Non-tuberculous mycobacteria

Likely organisms	Notes
Mycobacterium avium complex and *Mycobacterium abscessus*	Seek expert advice CPIT with ID/Microbiology input Local guidance available here