ANTIBIOTIC TREATMENT FOR CYSTIC FIBROSIS

Report of the UK Cystic Fibrosis Trust Antibiotic Working Group

Third Edition

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<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
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<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
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<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
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<td>2++</td>
<td>High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
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<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
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<td>2-</td>
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Grades of recommendations

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<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</td>
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<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++</td>
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<td>Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+</td>
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ABBREVIATIONS

AAD Adaptive aerosol delivery system
ABPA Allergic bronchopulmonary aspergillosis
ATS American Thoracic Society
Bcc  *Burkholderia cepacia* complex
GFR Glomerular filtration rate
IV  Intravenous
MAC  *Mycobacterium avium* complex
MCBT Multiple combination bactericidal testing
MRSA  Meticillin-resistant *Staphylococcus aureus*
MSSA  Meticillin-sensitive *Staphylococcus aureus*
MU  Megaunits
NAG  N-acetyl-ß-D-glucosaminidase
NTM  Non-tuberculous mycobacteria
RCT  Randomised controlled trial
SCV  Small colony variant
TBA  Tracheobronchial aspergillosis
TIM  Target inhalation mode
TSI  Tobramycin solution for inhalation

**Abbreviations for timing of administration**

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SUMMARY

- All young children with cystic fibrosis (CF) identified by newborn screening, or diagnosed clinically, should be started on continuous anti-staphylococcal antibiotic prophylaxis with flucloxacillin (continued until 3 years).

- Samples of respiratory secretions (sputum or cough swab) should be sent for bacterial culture from CF patients at every medical contact. Approved laboratory techniques for CF organisms should be followed and the results acted on promptly.

- When *Pseudomonas aeruginosa* is found in respiratory secretions in a CF patient who was previously free of *P. aeruginosa* or who has never had the organism, then they should receive an appropriate eradication regimen in a timely fashion.

- All CF patients with chronic pulmonary infection with *P. aeruginosa* should have long term nebulised anti-pseudomonal therapy, unless contra-indicated.

- A six month trial of oral azithromycin should be considered in patients who are deteriorating on conventional therapy, irrespective of their infection status.

- Pulmonary exacerbations in CF patients should be treated promptly with oral or intravenous antibiotics. Intravenous treatment must be used if the patient’s condition does not improve with oral treatment.

- Support with nutrition and physiotherapy should be intensified during exacerbations. Home intravenous treatment is useful for some but this should be tailored to the needs of the patient and family.
1. THE USE OF ANTIBIOTICS IN CYSTIC FIBROSIS

1.1 Introduction

Antibiotic therapy for patients with CF is directed at preventing, eradicating, or controlling respiratory infections. The prompt use of effective antibiotics in these situations has been a major reason for the decreased respiratory morbidity and increased longevity seen over the last several decades. Without antibiotic treatment the infant with CF is at risk of early infection and inflammation becoming established [2+] and ultimately progressing to fatal respiratory failure.

1.2 Antibiotics for prophylaxis of infection

Prophylactic treatment is used to reduce the prevalence of *Staphylococcus aureus* infection and to prevent secondary bacterial infection when the patient has a presumed acute viral respiratory infection. There is no consensus on the use of daily oral flucloxacillin prescription for the former beyond early childhood.2 [1++] (section 4.1) The Copenhagen experience documents an increased incidence of new *Pseudomonas aeruginosa* acquisition in the winter “viral” months3 [2-] and it is generally agreed that viral induced respiratory tract damage may facilitate secondary bacterial infection. The use of oral antibiotics at the start of mild “viral” respiratory exacerbations should cover the possibility of secondary infection with common respiratory pathogens e.g. *Haemophilus influenzae* or *Streptococcus pneumoniae*. If the patient has chronic *P. aeruginosa* infection ciprofloxacin may be prescribed to try and prevent a Pseudomonas-associated deterioration. The additional antibiotic is taken until the patient returns to his/her previous condition even if this takes two or three weeks. If the new symptoms (most important being a new cough) do not settle a different oral antibiotic or intravenous antibiotic treatment, and the need for further cultures and a chest X-ray, should be considered.

1.3 Antibiotics to eradicate infection

Patients with *P. aeruginosa* infection have a 2–3 fold increased risk of death over an 8 year period.4 [2+] Successful eradication can be achieved in approximately 80% of cases of new *P. aeruginosa* infection by various combinations of oral, inhaled and intravenous antibiotics. There is no consensus on the best combinations, dosage, or length of treatment courses.5 [2++] (section 5.2.1) Recent antibiotic treatments directed at eradication of early *Burkholderia cepacia* complex (Bcc) infection have been published, but have not been supported by large studies nor widely adopted.6,7 [3] Some CF centres attempt eradication of each new growth of *S. aureus* with combinations of oral anti-staphylococcal antibiotics.

1.4 Antibiotics to control infection

Inhaled and intravenous antibiotics are used to control infection. The former is recommended for patients with chronic *P. aeruginosa* infection and will preserve lung function and decrease the need for additional intravenous treatments.8 [1a] The majority of patients are treated with twice daily colistin or tobramycin solution for inhalation. The latter drug is administered on a one month on/one month off regimen (section 5.2.2).

Acute respiratory exacerbations are usually treated early with two intravenous antibiotics that have different mechanisms of action, to reduce the potential for encouraging bacterial resistance from frequent therapy and to benefit from any potential antibiotic synergy. The standard treatment course is for two weeks (section 6.5). There is no consensus on the use of antibiotic susceptibility test results as a basis for antibiotic choices (section 6.4.2iii).
In 1989 the Copenhagen centre recommended a regimen of elective intravenous antibiotic treatments for two weeks every three months to control chronic *P. aeruginosa* infection. This regimen resulted in a better five year survival.\(^9\)\(^②\) It is now suggested that only patients requiring this frequency of antibiotic administration to maintain clinical stability should be considered for such treatment. For other patients the risks of antibiotic induced toxic effects on renal function, hearing and balance, may outweigh the possible benefits of three monthly treatments. With contemporary management most patients do not require four intravenous antibiotic courses annually to maintain clinical stability. Moreover, patients are living much longer and therefore the potential for serious adverse events from a lifetime of frequent antibiotic treatments is significantly increased. A greater frequency of antibiotic use also increases the risk of patients developing antibiotic hypersensitivity reactions\(^10\)\(^②\) and the risk of bacterial resistance.\(^11\);\(^12\)\(^②\) The health service costs of elective treatment and the extra costs incurred by hospitalisation for the patient and relatives are other important considerations.

1.5 The use of antibiotics in CF differs from their use in unaffected individuals

The general principle is to have a low threshold for antibiotic prescription and to treat any bacterial pathogen isolated from respiratory samples. Upper respiratory cultures are often all that are available, especially from children, but are not always reliable indicators of lower respiratory tract infection. Positive cough and throat swabs usually prompt antibiotic treatment, especially when new symptoms are present. This differs from the approach taken with the general population in whom most respiratory infections will resolve without antibiotics. In contrast, in CF, chronic and progressive lower respiratory tract infection may start early, and is possibly inevitable, unless antibiotic treatment is used.

Patients with CF often require higher doses for longer periods because of differences in antibiotic clearance and distribution, which may be further altered according to the severity of the respiratory infection.\(^13\)\(^④\) Because of the higher aminoglycoside doses used, extra care must be taken with monitoring serum levels. These should be measured as a minimum at the beginning of each week of therapy.

Frequent intravenous antibiotic treatment increases the incidence of drug-associated hypersensitivity reactions. Antibiotic tolerance can be induced by following desensitisation protocols. If a reaction occurs during desensitisation the procedure should be stopped and no further attempts should be made to administer that antibiotic to the patient.

1.6 Home intravenous antibiotic treatment (HIVT)

Implantable venous access devices should be considered when venous access is difficult and frequent intravenous therapy is necessary. The widespread use of HIVT has been a major factor in improving the daily lives of many patients with CF. HIVT protocols should maximise patient safety through proper instruction and supervision of the patient and caregiver. Patients should have an anaphylactic kit at home and be confident in the knowledge of when and how to use it. All patients should have access to a Specialist CF Nurse when self-treating at home.\(^14\)\(^④\) Once daily aminoglycosides are safe and effective\(^15\)\(^①++\) and especially convenient for home based therapy.

1.7 Non-bactericidal effects of antibiotic treatments in CF

There is increasing evidence for macrolide use as part of the standard treatment of patients with CF. The 14-membered and 15-membered macrolides, such as erythromycin, clarithromycin, and azithromycin have anti-inflammatory properties, and interfere with adherence of *P. aeruginosa* to epithelial cells and the biofilm mode of growth.
In adults treatment with azithromycin has been associated with significantly fewer courses of intravenous antibiotics, maintenance of lung function, reduction in median C-reactive protein levels, and improvement in quality of life scores.\textsuperscript{16} [1+] In children the use of azithromycin was associated with a significant but modest (5.4\%) group response in FEV1 and less use of oral antibiotics, although five of 41 patients had a clinically important deterioration. The full benefit of treatment was seen two to four months after the commencement of therapy.\textsuperscript{17} [1+] More recent studies have all confirmed the benefits of azithromycin treatment.

When macrolides are used long term it is important to maintain microbiological surveillance for macrolide-resistant strains of \textit{Staphylococcus aureus}\textsuperscript{18} [3] and non-tuberculous mycobacteria.

\subsection*{1.8 New antibiotic challenges}

Probably as a result of more successful treatment of classic bacterial infection in CF we are increasingly faced with multi-resistant isolates of \textit{Pseudomonas aeruginosa} and innately resistant organisms such as \textit{Stenotrophomonas maltophilia}, \textit{Achromobacter (Alcaligenes) xylosoxidans}, and non-tuberculous mycobacteria. Meticillin-resistant \textit{Staphylococcus aureus} is a growing problem. The optimal treatment for these resistant bacteria, or even if treatment is always necessary, is not known. All may be associated with either asymptomatic infection, or respiratory exacerbations in those persistently infected with large numbers of these organisms (section 7).

Fungal infections similarly have become more prevalent in recent years. Infection with \textit{Aspergillus} sp. has long been recognised as a problem in CF, usually presenting as allergic bronchopulmonary aspergillosis. Recently it has been suggested that Aspergillus infection can cause respiratory exacerbations by stimulating a fungal-associated bronchitis that responds to specific antifungal therapies.\textsuperscript{19} [3] Other fungi are increasingly recognised as complicating CF care e.g., \textit{Scedosporium apiospermum} and \textit{Wangiella (Exophiala) dermatitidis}.

\subsection*{1.9 Non-antibiotic protection against infection}

It is important to acknowledge that antibiotic treatment is just one part of the fight against respiratory infection. Patient segregation according to respiratory culture results will minimise cross-infection with \textit{Burkholderia cepacia} complex.\textsuperscript{21} [3] Children should receive the national programme of childhood immunisations. \url{http://www.immunisation.nhs.uk/Immunisation_schedule} The national schedule now includes immunisation against pneumococcus at 2, 4 and 13 months, with the heptavalent conjugate vaccine. The 23 valent vaccine can be offered to older patients with CF and annual influenza immunisation is also recommended. [D]

\subsection*{1.10 Conclusion}

 Antibiotics are one of the most important components of present-day CF treatments which have been responsible for an increase in median survival to almost 40 years. The quality of life, length of survival, and cost of care largely depend on the success or failure of antibiotic treatment to eradicate the initial and subsequent \textit{Pseudomonas aeruginosa} infections in early childhood, and by the subsequent antibiotic treatment of respiratory infective exacerbations.

To determine the best antibiotic treatment regimens and to ensure that all people with CF benefit from them, the Cystic Fibrosis Trust has updated the Report of the Antibiotic Group. The views set out in this Report are those agreed by this panel of experts. The recommendations are believed to represent best treatment, but Specialist CF Centres may wish to interpret them in the light of their own experience and the perceived needs of each patient on a day-to-day basis.
We hope this third edition of the document will continue to provide accessible up-to-date information and guidance for those with the considerable responsibility for advising on the treatment of patients with CF.

1.11 References


2. MICROBIOLOGY AND ANTIBIOTIC THERAPY – A CF PERSPECTIVE

2.1 Introduction

The microbiology of the CF lung is complex and challenging. Treatment of early infections with antibiotics may lead to resolution of symptoms and clearance of the bacteria. Eventually however most patients become chronically infected with bacteria (i.e. the bacteria persist in the airways even when treatment with antibiotics has improved the patient’s condition). In chronic infection, bacteria such as *Pseudomonas aeruginosa* undergo major genetic adaptations presumably in order to survive in the damaged airways in CF by evading the patient’s immune response and resisting antibiotic treatment.\(^1\);\(^2\) When grown in the laboratory, bacteria from chronic infections have different features from those causing acute infections. The *in vitro* tests devised to measure antibiotic susceptibility for acute infections such as *Streptococcus pneumoniae* community acquired pneumonia or *Staphylococcus aureus* wound infection may not be suitable for guiding the treatment of acute exacerbations of chronic pulmonary infection in CF. This may explain why microbiology results from diagnostic laboratories, in particular for antibiotic susceptibility, do not always correlate with the clinical experience of using different antibiotics in these patients.

2.2 Pathogens

It had been thought that a limited spectrum of potential respiratory pathogens was seen in CF, but increasing numbers of other species are being recognised. Few of these however cause respiratory tract infection in patients with normal lungs.\(^3\) *S.aureus* is a frequent isolate and may be cultured early in infancy and *Haemophilus influenzae* is most often found in childhood. The common strains of *H.influenzae* in lung disease are mostly non typeable and are not prevented by vaccines for capsule type B. *S.pneumoniae* is occasionally isolated from young CF patients but is unusual. *Paeruginosa* is the most common pathogen in CF.\(^4\) It may be cultured early in the course of disease but is often cleared with treatment with an oral quinolone such as ciprofloxacin plus an inhaled antibiotic (section 5.2.1). After the initial isolate, *Paeruginosa* may be found intermittently in respiratory secretions but eventually chronic infection is established in most patients. This is associated with a faster deterioration in lung function. Infection is characterised by persistence of the bacteria and repeated episodes of worsening of infection (exacerbation) that usually respond to a course of antibiotics (sections 4 & 6).

Other gram-negative bacteria can also infect or colonise the lung, usually later in the progression of CF. The most clinically significant has been the *Burkholderia cepacia* complex.\(^4\) This complex of species is almost unique to CF and a rare immune disorder, chronic granulomatous disease. *B.cepacia* complex consists of a range of species of differing pathogenic potential of which *B.cenocepacia* and *B.multivorans* are the most common (section 7). *B.cepacia* complex had a major impact in the 1980s and 90s with outbreaks leading to many deaths. The number of patients with *B.cepacia* complex has declined rapidly following measures to stop person to person spread. The impact of other species of Burkholderia, and of *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, *Ralstonia* (formerly *Pseudomonas*) *pickettii* and *Pandorea apista* on individuals and their propensity for cross infection still warrants further study (section 7). Recent reports from reference laboratories indicate that many gram-negative bacteria in CF are incorrectly identified using standard laboratory tests. Some are colistin resistant and may be mis-identified as *Burkholderia* sp.\(^5\);\(^6\) It is important that bacteria are carefully identified when treating infection as the range of antibiotics that may have activity are species specific as are the growth conditions required for testing antibiotic susceptibility in the laboratory.

More recently there has been a recognition that other bacterial species – usually considered part of the normal oral flora, including anaerobes – are found in significant numbers in the sputum of patients with CF.\(^7\);\(^8\) The presence of bacteria in the lung does not necessarily imply a direct pathogenic effect.
These bacteria can be harmless commensals or interact with other bacteria influencing their growth or behaviour. For example, a viridans streptococcus and a coagulase-negative staphylococcus from CF sputum were found to up-regulate genes involved in pathogenicity in *P. aeruginosa*.9

Infections with non-tuberculous mycobacteria, in particular *Mycobacterium abscessus* and the *M. avium intracellulare* complex are a major therapeutic challenge in CF (section 7). Aspergillus sp. may cause an immuno-pathological reaction – allergic broncho-pulmonary aspergillosis (section 7). The role of *Aspergillus* sp. and other filamentous fungi such as *Scedosporium apiospermum* in other types of fungal disease still awaits clarification.

### 2.3 Variability

Chronic infection with *P. aeruginosa* is characterised by the appearance of different forms of bacterial colony (morphotypes) including mucoid (hyper alginate producers) and small colony variants (SCV) – also known as dwarf colonies. SCVs are slow growing, so may be missed in the routine laboratory and often have more antibiotic resistance than other isolates.10 SCVs appear to adhere well to surfaces and may be involved in the development of biofilms (see below). Phenotypic variation seen in organisms of the same genotype is not just limited to colonial variation. The degree of antibiotic susceptibility can also vary between bacteria of the same genotype and even the same morphotype of *P. aeruginosa* in a single patient’s sample.11;12 One consequence of this is that antibiotic susceptibility testing *in vitro* is poorly reproducible (different results can be obtained, depending upon which bacteria are tested). Different colony types of *S. aureus* are seen in single samples from chronic infection in CF, not the wide variety of morphotypes found in *P. aeruginosa* but classical colonies mixed with slower growing SCVs with varied antibiotic susceptibility.13 *B. cepacia* complex can also grow as different morphotypes and show a range of antibiotic susceptibility.14

### 2.4 Hypermutators

Bacteria have systems to reduce the number of mistakes made when DNA replicates (“proof reading”). Hypermutators are bacteria with mutation in their DNA repair or error avoidance genes leading to an increase in the intrinsic rate of mutation. Mutations can be deleterious or advantageous and it is thought that the repeated use of antibiotics in CF maintains a selection pressure that encourages hypermutators.15 An early study showed that 37% of CF patients chronically infected with *P. aeruginosa* harboured mutator strains, one of the highest prevalence in a natural system.16 Mutators are also common in other chronic lung diseases (non CF bronchiectasis and severe COPD) but rare in acute infections.17 Hypermutator strains of *H. influenzae*, and *S. aureus* have also been found more frequently in CF than in other conditions.18;19 The practical impact of a high rate of spontaneous mutation is that if the population of bacteria is large enough in the CF lung, a sub-population of bacteria with a mutation giving resistance to an antibiotic is likely to be present even before treatment starts, and will be selected if the patient is treated with that antibiotic on its own.20 Data from *in vitro*, animal and clinical studies showed the selection of resistant strains with mono-therapy even before hypermutators were described in CF. On this basis, expert consensus groups have recommended that combination antibiotics should be used to treat *P. aeruginosa*.21 [C]

### 2.5 Biofilms

In acute infections it is thought that bacteria are free-floating (“planktonic”); they may adhere to surfaces but do not form a structured aggregate. In contrast, biofilms comprise groups of bacteria embedded in an acellular matrix usually attached to a surface. In CF the surface is the damaged wall of the airway and the matrix consists of bacterial products (predominantly alginate) plus material derived from the patient’s cells. In chronic infection in CF, *P. aeruginosa* and the *B. cepacia* complex are thought to grow in biofilms in chronic infection. Although *H. influenzae* is not thought to cause
chronic infection in CF, fragments of biofilm have been found in BAL from young CF patients with infection with *H. influenzae*. Biofilms of *H. influenzae* can also form on epithelial cells *in vitro*.22

Bacteria in biofilms are physiologically diverse showing a range of adaptations to the different micro-environments in the complex biofilm structure.23 They are more resistant to many antibiotics compared with when growing planktonically.24;25 There are several explanations for this. Although there are physical channels that should allow free diffusion of antibiotics, interactions between the antibiotic and the amorphous material in the biofilm may protect the bacteria. Micro-organisms respond to the varied conditions such as areas of oxygen deficit or local nutrient limitation by slowing growth and changing metabolism and these can lead to antibiotic resistance.26 For example, the efficient transport of tobramycin into the bacterium cell relies on oxidative metabolism and is therefore reduced in an anaerobic environment; antibiotics that act on the cell wall are only effective if the bacteria are actively dividing. Conversely *P. aeruginosa* growing in a simple biofilm *in vitro* was found to be susceptible to azithromycin at levels achievable in the patient, whereas in conventional tests it is resistant.27 Simpler techniques for testing antibiotic susceptibility in a biofilm *in vitro* have been proposed and their clinical relevance is being evaluated.24;26 Understanding what happens in a biofilm in chronic infection is a rapidly developing area and may bring new insights into the pathogenesis of infection in CF.28

2.6 Treatment of multi- and pan-resistant bacteria

The use of antibiotics in CF has significantly improved the quality of life and survival, but at a cost. Many of the gram-negative bacteria that infect patients with CF are intrinsically resistant to a range of antibiotics and the prevalence of bacteria with newly acquired resistance has increased with improved life expectancy.29 Resistance rates in *P. aeruginosa* in the UK have increased dramatically with approximately 40% resistant to 2 or more antibiotics in one study.30 Much resistance in *P. aeruginosa* arises from mutation rather than by acquiring resistance genes from other bacteria. Bacteria can produce enzymes that destroy antibiotics, modify the antibiotic target site or develop systems to pump antibiotics out of the cell (efflux). The definitions of multi- and pan-resistant bacteria used in the literature vary; the most frequent are those from the North American CF Foundation 1994 consensus conference.31 For this, the CFF consider three main classes of antibiotics: the aminoglycosides (e.g. tobramycin), cell wall-active agents – to include penicillins, cephalosporins, penems (e.g. meropenem) and quinolones (e.g. ciprofloxacin). Multi-resistance is defined as resistance to 2 classes and pan-resistance to all 3. The definition however excludes colistin. The selection of antibiotics to treat resistant strains is made more difficult because allergy is common in CF and further limits the number of antibiotics that can be used.

Combinations of antibiotics have been shown to be synergistic *in vitro*, offering treatment options for multi-resistant strains of *P. aeruginosa*, *A. xylosoxidans* and *S. maltophilia*,32-34 however synergistic combinations *in vitro* were rare for the *B. cepacia* complex.35 There are different ways of testing combinations such as using checkerboard dilutions, time kill curves, multiple combination bactericidal test (MCBT), but there is no agreed “gold standard” and the results vary depending on the technique used.36 A Cochrane review (currently in progress) has highlighted the paucity of information on the clinical role of testing antibiotic combinations to find effective treatment for resistant bacteria in CF.37 Only one prospective study has looked at this, using MCBT.38 In this multi-centre study, 132 patients with multi-resistant isolates of *P. aeruginosa*, *B. cepacia* complex, *A. xylosoxidans* and *S. maltophilia* were treated for a pulmonary exacerbation. Using the MCBT to determine the choice of antibiotics was no better than conventional antibiotic testing methodology. Clinical strategies guided by appropriate laboratory testing are therefore still needed to tackle resistant infection.
2.7 Clinical relevance of in vitro susceptibility testing

Early in CF, most bacteria are susceptible and antibiotics can successfully treat infection. Once a patient has a chronic infection, it is very difficult to clear the bacteria from the lung, even if they appear antibiotic susceptible \textit{in vitro}. In addition, the experience of CF clinicians is that the results of antibiotic susceptibility tests do not always correlate with the way the patient responds to the empirical antibiotics used to treat an acute exacerbation.

An early study showed that treating \textit{P.aeruginosa} with antibiotics effective \textit{in vitro} led to a good clinical and bacteriological response.\textsuperscript{39} Others have however shown that patients may still respond well to antibiotics even if the bacteria are resistant \textit{in vitro}.\textsuperscript{40} In one study, the improvement in lung function of 77 CF patients to ceftazidime and tobramycin did not relate to the Minimal Inhibitory Concentration (MIC) of the antibiotics for \textit{P.aeruginosa} in the sputum taken closest to an exacerbation.\textsuperscript{41} It is unclear if a clinical response in spite of \textit{in vitro} resistance is due to a lack of “fitness” in the resistant forms,\textsuperscript{42} or whether antibiotics are acting below the MIC to affect pathogenicity factors such as motility, toxin and alginate production and the formation of biofilms.\textsuperscript{12;43;44}

The pathogenic role of \textit{S.maltophilia} is uncertain, therefore a poor response to therapy directed at this organism may be because the wrong infection is targeted. There is little published on the more recently recognised gram-negative bacteria such as \textit{A.xylosoxidans}, \textit{R.pickettii} and \textit{P.apista} and more information on bacterial susceptibility and approaches to treatment are needed.

\textit{P.aeruginosa} in a single sputum consists of a mixed population with a wide variation in antibiotic susceptibility. As a result, antibiotic susceptibility testing in the routine laboratory testing is poorly reproducible with resistance isolates easily missed. This can be improved by increasing the number of bacteria tested from each sputum,\textsuperscript{11} or culturing sputum on agar containing antibiotics.\textsuperscript{45} Less is known about the limitations of the current approach to antibiotic susceptibility for other species, however small colony variants of \textit{S.aureus} are more resistant to antibiotics and may be missed in the routine laboratory.

The nationally agreed “breakpoint” antibiotic concentrations are used in the clinical laboratory to sort resistant from susceptible bacteria.\textsuperscript{46} A breakpoint used as an epidemiological cut-off to identify resistance mechanisms may not be relevant to the clinical situation if, as in CF, the infection is in a site such of poor antibiotic penetration or activity such as the lung. For example it has been shown that the optimum pharmaco-dynamic indices are not achieved for common anti-pseudomonals in serum or sputum.\textsuperscript{47} Conversely, current breakpoint concentrations are not relevant for inhaled antibiotics where the lung concentrations are far higher.\textsuperscript{48}

2.8 Future directions in CF microbiology

Are there additional tests currently used in research that should be adopted by the clinical laboratory? It may be important to identify hypermutators because of the risk of resistance developing on treatment. The limitations of testing for synergy for known multi or pan resistant bacteria have already been described and their role in clinical practice is under debate.\textsuperscript{33;49} Current laboratory methods for testing antibiotic susceptibility are designed for acute infections with free-floating (planktonic) strains and work is in progress to find an \textit{in vitro} test that may be more relevant to the action of antibiotics in the biofilms of the CF lung.\textsuperscript{27} Although some studies have showed that antibiotics reduce the number of bacteria in sputum,\textsuperscript{39;40} others have shown a good clinical response with no significant change in bacterial numbers. This questions the relevance of antibiotic susceptibility testing \textit{in vitro} that measure the ability of antibiotics to inhibit the growth of bacteria or to kill them.
Finally, bacteria other than classical respiratory pathogens found as mixed populations in significant numbers in CF sputum, (oral-type flora and anaerobes) may influence the growth or behaviour of the assumed pathogens. Antibiotics that do not have activity against the classical pathogens could still have an effect by their action on these microbial “co-factors”.

The publication of recent research has greatly increased our understanding of the ecology of the CF lung but the role of susceptibility testing in the microbiology laboratory for selecting antibiotics to treat infections in CF has become less rather than more clear. Although there were originally thought to be a limited number of organisms that caused symptomatic infection and lung damage in CF, the microbial ecology of the CF lung has been shown to be more complex, both in the variability of individual pathogens and in the mixed population of species that can occur. The challenge to microbiologists is to review the established methodologies and explore new ways of supporting the CF clinician in optimising management of CF infection. Lessons learned from this complex microbial system may help improve the management of other chronic infections both in the lung and elsewhere.

2.9 References


3. IDENTIFICATION OF LOWER AIRWAY INFECTION

3.1 Introduction

Identification of lower respiratory infection in individuals with CF represents a challenge. Young children may not expectorate sputum, even when they have a wet cough. Many patients with CF have little lung damage and so do not have sputum to expectorate. However, in order to avoid progressive lung damage and bronchiectasis, it is essential to identify and treat lower respiratory infection at an early stage. It is a paradox in CF that as treatment of pulmonary infection improves, diagnosis of such infection becomes more difficult. There are a number of situations where diagnosis of pulmonary infection is important, for different reasons.

- The asymptomatic patient without chronic airway infection. Identification of *Pseudomonas aeruginosa* from the respiratory culture of asymptomatic patients facilitates prompt treatment, which results in eradication in a significant number.\(^1\,^2\) Not treating *P. aeruginosa* results in chronic airway infection.\(^1\,^3\,^4\,\)\(^6\)

- The symptomatic patient without chronic airway infection. The identification of airway infection in the symptomatic patient facilitates appropriate treatment.\(^7\)

- The patient with chronic airway infection. In these patients, regular culture of respiratory samples facilitates:
  - Monitoring individuals for change in sensitivity patterns\(^8\,^9\)
  - Identification of new strains/pathogens in an individual\(^10\,\)\(^12\)
  - Identification of emergence of epidemic strains in a clinic population\(^8\,^13\,^14\)

3.2 Methods to identify airway infection

In the patient who is not productive of sputum, the following microbiology specimens can be collected. The advantages and disadvantages of each are summarized in table 1.

- Cough swab
- Cough plate
- Oropharyngeal culture (throat)
- Laryngeal or naso-pharyngeal aspirate
- Exhaled breath condensate
- Induced sputum following hypertonic saline
- Bronchoalveolar lavage
- Serology (functional *P. aeruginosa* antibodies)

In the patient who does produce sputum, a sputum sample is likely to be the best clinical specimen, for practical purposes.
Table 1: Methods to identify lower airway infection
(patient who does not produce sputum)

<table>
<thead>
<tr>
<th>Method</th>
<th>Summary of evidence/comments</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough swab (coughing directly onto a moist or dry swab)</td>
<td>Limited evidence of validity. Poor sensitivity and unknown specificity</td>
<td>15–17</td>
</tr>
<tr>
<td>Cough plate (coughing directly onto a plate of culture medium)</td>
<td>Limited evidence of validity (conflicting reports). Potentially good acceptability</td>
<td>17;18</td>
</tr>
<tr>
<td>Oropharyngeal culture (or throat swab)</td>
<td>Reasonable specificity (&gt;90%) but poor sensitivity for identifying <em>P. aeruginosa</em> lower airway infection</td>
<td>19–25</td>
</tr>
<tr>
<td>Laryngeal or naso-pharyngeal aspirate</td>
<td>Limited evidence of validity, established technique in many CF centres</td>
<td>14;25</td>
</tr>
<tr>
<td>Exhaled Breath Condensate</td>
<td>Not clinically relevant; research tool</td>
<td>26;27</td>
</tr>
<tr>
<td>Induced sputum following nebulised hypertonic saline</td>
<td>Emerging clinical tool with potential for identification of airway infection in the non-productive patient. More studies required to determine validity</td>
<td>16;28–32</td>
</tr>
<tr>
<td>Broncho-alveolar lavage (during bronchoscopy)</td>
<td>Considered “gold standard” in comparative studies. Requires anaesthesia or sedation. Contamination of scope with upper airway pathogens reduces specificity. Localised infection in lungs may reduce sensitivity. Potential for cross infection</td>
<td>7;24;33–40</td>
</tr>
<tr>
<td>Serology (functional anti-<em>P. aeruginosa</em> antibodies)</td>
<td>May have role in recognising early <em>P. aeruginosa</em> infection in non-productive patients but unclear sensitivity and specificity. More studies required to determine validity</td>
<td>41–44</td>
</tr>
</tbody>
</table>

I. Sensitivity The ability of the test to detect true positive
II. Specificity The ability of the test not to recognise false negative results

3.3 Laboratory techniques

The number of laboratory techniques available (both culture and molecular) has grown in recent years. A Consensus Guideline on Laboratory Techniques is expected to be published by the UK Cystic Fibrosis Trust towards the end of 2009. Table 2 summarises the advantages and disadvantages of some of the laboratory techniques currently available (some restricted to research laboratories). Please refer to the Consensus Guidelines on Laboratory Techniques when this becomes available for definitive advice.
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Culture techniques</th>
<th>Molecular techniques</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Common respiratory pathogens; a) Viral | a) Culture on appropriate cell-lines  
  b) Shell vial culture                | a) Antigen detection (ELISA, immunofluorescence)  
  b) Genome detection (reverse transcription-PCR for RNA viruses and PCR for DNA viruses) | Molecular techniques are more sensitive and rapid than culture. (Genome detection more sensitive than antigen detection). |
| b) Bacterial                     | Standard culture techniques (including enriched media for *Haemophilus influenzae*, (Roman X and V growth factors)) | PCR assay on sputum or cultured bacteria for MRSA                                        | Routine                                                                |
| *P. aeruginosa*                  | Culture on both enriched (e.g., blood agar) and selective media                      | Direct PCR on sputum or other respiratory samples.  
  PCR or pulsed field gel electrophoresis of macro-restricted chromosomal DNA required for detection of epidemic clones | PCR is a research tool. It has the disadvantage of not giving antimicrobial susceptibility patterns. |
| *Burkholderia cepacia complex*   | Culture on Burkholderia specific media is essential                                 | PCR required for species assignment and identification of epidemic clones                | Undertake on a regular basis on all patients                             |
| Atypical mycobacteria            | Samples prepared by appropriate preprocessing (e.g., Petrov’s method) and cultured on Lowenstein Jensen slopes for up to 12 weeks | Not available for detection but valuable for identification                             | Consider in patients not responding to standard therapy                 |
| Other atypical respiratory pathogens | Potential pathogens such as; *Achromobacter xylosoxidans*, *Inquilinus* sp., *Pandorea apista* and *Stenotrophomonas maltophilia*, will grow on blood agar and MacConkey agar as well as the selective media for *P. aeruginosa* and some on the Burkholderia selective media. The laboratory will need to be asked to look for them | PCR is not available for detection but is valuable for identification of genus and species | Consider in patients not responding to standard therapy                 |
| Anaerobic pathogens              | Culture on appropriate media (e.g., blood agar, fastidious anaerobe agar) under anaerobic conditions | Not available                                                                          | Consider in patients not responding to standard therapy                 |
| Fungi (e.g., *Aspergillus* sp.)   | Culture on Sabourad’s agar (will also grow on blood agar)                            | Not available                                                                          | Undertake on a regular basis on all patients                             |
3.4 Recommendations for identification of lower airway infection in CF

- **Standard methods to identify infection should be undertaken at each hospital visit (8 weekly or more frequently) and at times of respiratory exacerbation [B].**

- **In the patient who does not produce sputum, other methods should be used to identify lower airway infection. Current evidence does not strongly support one particular method (Table 1) [B].**

- **Surveillance of a clinic population for emergence of epidemic strains should be undertaken regularly and in partnership with an experienced microbiology team [B].**

3.5 References


4. ORAL ANTIBIOTICS IN CYSTIC FIBROSIS

We are grateful to Sian Edwards (Royal Brompton Hospital) for her assistance in writing this section.

4.1 Introduction

In the absence of appropriate antibiotic treatment, the abnormal respiratory secretions of the patient with CF soon become infected with any or all of *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Eradication of a particular organism is likely easier in the early stages of infection; this may be achieved by using an intravenous antibiotic when the same drug given orally has failed – even though the organism appears to be fully sensitive to the oral drug.

4.2 Treatment of meticillin-sensitive *Staphylococcus aureus* (MSSA) infection

MSSA is clearly a significant pathogen in CF patients. The aim of treatment is to prevent infection with, or eradicate MSSA infection from the respiratory tract.

4.2.1 Prophylactic anti-staphylococcal antibiotics (Option 1) (section 8.1)

A Cochrane review has shown that continuous, anti-staphylococcal antibiotic prophylaxis, with a narrow spectrum antibiotic such as flucloxacillin, from diagnosis until the age of 3 years, is effective in reducing the incidence of infection with MSSA.\(^1\)\(^{[1++]}\) There is currently no evidence that this regimen increases the incidence of *P. aeruginosa*. However, an improvement in clinical outcomes with prophylaxis has not been shown. This is in part due to the lack of good data from randomised controlled trials, which have rightly been called for by the reviewers. The main safety concern raised is selection for *P. aeruginosa* infection with the use of broad spectrum antibiotics such as cephalexin.

A US CF Foundation multicentre controlled trial of long-term cephalexin included 209 children less than 2 years old with mild chest involvement. Only 119 children finished the study. After 5 years, although the treated children failed to demonstrate any significant clinical advantage, they had fewer respiratory cultures positive for *S. aureus* (6% in the cephalexin group versus 30% of controls) but more were positive for *P. aeruginosa* (26% of the cephalexin group versus 14% of controls).\(^2\)\(^{[1-]}\) Evidence from the German CF Registry also supports this finding.\(^3\)\(^{[2-]}\) Thus the safety of prophylactic, broad spectrum, oral cephalosporins must be questioned although there is currently no evidence to suggest that a narrow spectrum antibiotic, such as flucloxacillin (widely used in the UK) poses such a risk.

4.2.2 Intermittent antibiotics (Option 2)

An alternative approach to long-term flucloxacillin from diagnosis is a two to four week course of one or two appropriate antibiotics whenever MSSA grows from respiratory cultures. There are no formal trials of this approach, nor can particular doses or duration be recommended.

4.2.3 Secondary prevention of MSSA infection (Option 3)

Clinics which do not prescribe routine prophylactic anti-staphylococcal antibiotics will consider prescribing these long-term if MSSA is isolated repeatedly. There is no evidence to guide the clinician when to institute this policy, or with what antibiotic regimen, or for how long it should be continued.
4.2.4 Recommendations for treatment of MSSA in CF

- Continuous, anti-staphylococcal antibiotic prophylaxis, with a narrow spectrum antibiotic such as flucloxacillin, may be used, from diagnosis until the age of 3 years, to reduce the incidence of infection with MSSA. The prophylactic dose used in previous clinical trials is 125 mg twice daily [A].

- If MSSA grows while the patient is receiving flucloxacillin, consider patient adherence and increase the flucloxacillin to 100 mg/kg/day and add a second oral anti-staphylococcal antibiotic for two to four weeks (sodium fusidate, or rifampicin) (section 8.2). Check cultures after treatment. If clear, continue long-term prophylactic flucloxacillin [D]. For patients who are allergic or intolerant to penicillins then an alternative antibiotic should be used. The choice is determined by the antibiotic sensitivity pattern of the organism and the age of the patient (e.g. tetracyclines should be avoided in children under 12 years).

- If cultures are still positive after 2 weeks of 2 antibiotics to which the organism is sensitive continue treatment for another 4 weeks. Culture every week if possible. If the patient is unwell and still growing MSSA, give a course of intravenous antibiotics (section 6.4.1). Two antibiotics, to which the organism is sensitive, should be used but in practice it may be easier to give one of these orally (e.g. fusidic acid or rifampicin) [D].

- If MSSA remains even after a course of IV antibiotics continue with long-term flucloxacillin (100 mg/kg/day) and also check patient’s adherence to treatment. Treat with an additional anti-staphylococcal antibiotic whenever there is any increase in the symptoms and signs and always try to include an anti-staphylococcal antibiotic with any subsequent IV courses of treatment [C].

- Broad spectrum cephalosporins should not be used as treatment for MSSA [B].

- Macrolides cannot be assumed to provide effective empirical treatment for MSSA because macrolide resistance is increasingly common [D].

- Whatever regular regimen is chosen, any upper or lower airway isolate of MSSA is treated with a course of a new anti-staphylococcal regimen for two to four weeks and a further respiratory specimen obtained at the end of treatment to ensure the organism has been eradicated [C].

4.3 What is new since the last guidelines?

4.3.1 Use of linezolid

The oxazolidinone antibiotic linezolid is highly active against a wide range of gram-positive organisms; in the context of CF, MRSA and MSSA are particularly relevant. It is expensive, and there is significant risk of toxicity, including skin rashes, blood dyscrasias, and there are now reports of optic atrophy with courses >28 days. Blood pharmacokinetic studies in adults with CF showed levels similar to other populations after intravenous therapy, there was no need for higher dosing. In an adult with CF, plasma levels were the same whether linezolid was given orally or intravenously. Oral administration in standard doses gives good sputum levels. All the current evidence for the use of linezolid in CF is anecdotal. It has been reported to be effective in eradication of MRSA. [3] Rarely, linezolid resistant organisms may emerge during treatment. This was a case report in a child who had received repeated, prolonged, low dose linezolid, underscoring the need for proper dosing regimens.
4.3.2 Recommendations for use of linezolid in CF (section 8.3)

- **Linezolid should be reserved for treatment of refractory MRSA (2–4 week courses) [D].**
- **Monitoring should be as for the non-CF patient; there is no evidence to suggest that special precautions are necessary. Frequent monitoring of blood count is recommended for all patients at risk of thrombocytopenia e.g., CF patients with splenomegaly [C].**
- **There is no advantage to intravenous therapy over oral therapy, and doses appropriate for the non-CF patient can be used [C].**

4.4 Treatment of *Haemophilus influenzae* infection

4.4.1 Introduction

The importance of this infection has been disputed, but most CF clinics would regard it as a significant pathogen. There is increasing evidence that non-typeable *H. influenzae* can form biofilms,11 lending weight to the argument that it is of pathogenetic significance. The aim of treatment is to eradicate *H. influenzae* infection and prevent chronic infection. There are no trials to demonstrate benefit from eradication of *H. influenzae* from respiratory cultures in CF, and no trials of any antibiotic regimen.

4.4.2 Recommendations for antibiotic use when *H. influenzae* is isolated (section 8.4)

- **If *H. influenzae* is isolated from acute or routine respiratory tract cultures at any time, even if the patient is apparently asymptomatic, an appropriate antibiotic is given for two to four weeks [D]. Suggested antibiotics include co-amoxiclav, or doxycycline (patients over 12 years only). Macrolide resistance is common and macrolides are not particularly effective against *H. influenzae*, even if it appears sensitive in the laboratory. Resistance to amoxicillin is also common.**
- ** Cultures should be repeated after treatment. If the cultures are still positive but the patient is well, note sensitivities and give further 2–4 weeks of an oral antibiotic [D].**
- **If cultures are still positive after one month, the patient should be considered for a 2-week course of IV antibiotics [D].**
- **If new symptoms have not cleared, even though the culture is negative, or if the clinical condition worsens at any time, a course of IV antibiotics is indicated [D].**
- **If cultures remain positive despite intensive treatment or there are frequent recurrences of *H. influenzae* positive cultures after courses of treatment, a long-term anti-*H. influenzae* antibiotic should be considered, analogous to the use of anti-staphylococcal prophylaxis. Cephalosporins should not be used (above [D]).**
4.5 Use of oral antibiotics at times of presumed viral colds or minor increase in respiratory symptoms

4.5.1 Introduction

Many clinics would prescribe a two to four week course of an oral antibiotic covering MSSA and *H.influenzae* with any increase in respiratory symptoms, even in the absence of a positive upper or lower airway culture. There is no evidence base for this practice.

4.5.2 Recommendations for upper respiratory (presumed) viral infections

With all colds, accompanied by a persistent cough or other lower respiratory symptoms, start an oral antibiotic which will cover both *H.influenzae* and *S.aureus* (e.g. co-amoxiclav) after sending a throat swab or sputum for culture. If the parent/patient has started taking an antibiotic, kept in reserve at home, then they should inform the Specialist CF Centre or Clinic that they have started treatment and send a specimen for culture. A supply of an antibiotic, chosen on the results of the patient’s previous culture results, can be given to keep at home for these occasions. After 2–3 days the parent/patient should check with the hospital clinic for the culture results. If the culture is positive, they should confirm that the organism is sensitive to the antibiotic that has already been started; if not, they should change to an appropriate antibiotic. Culture should be repeated after the course of antibiotics to confirm the absence of pathogens [D].

If new symptoms develop, e.g., a new cough, or a positive culture does not clear with appropriate oral antibiotic treatment, a course of IV antibiotics should be considered [D].

4.6 Treatment of early *Pseudomonas aeruginosa* infection

4.6.1 Introduction

The success of early identification and treatment in preventing *Paeruginosa* infection becoming established and chronic frequently determines the patient’s future quality of life and long-term survival. The aim of therapy is to eradicate *Paeruginosa* from the respiratory tract, thus avoiding the establishment of chronic infection. This section describes the potential role of orally active antibiotics in the management of infection with *Paeruginosa*. There is no doubt that the isolation of *Paeruginosa* from a patient previously culture negative should be treated energetically. [1+] Combinations of systemic and nebulised antibiotics have been selected by different centres. There is no evidence favouring any particular regimen.

4.6.2 Recommendations for the use of ciprofloxacin

- **Ciprofloxacin may be prescribed as part of the eradication regimen, for periods of up to 3 months. This is usually combined with a nebulised antibiotic. Eradication regimens for *Paeruginosa* are dealt with fully in section 5.2.1 [A].**
4.7 Treatment of patients chronically infected with *P. aeruginosa*

4.7.1 Introduction

In patients chronically infected with *P. aeruginosa* it is common practice to prescribe a 2-week course of ciprofloxacin for colds or mild exacerbations, with the aim of preventing more serious exacerbations and avoiding the need for intravenous treatment. There is no evidence from clinical trials to support this practice. Regular courses of ciprofloxacin have shown little benefit in chronically infected adults.

4.7.2 Recommendations for treatment of patients chronically infected with *P. aeruginosa*

- A 2-week course of ciprofloxacin may be given to patients with CF who are chronically infected with *P. aeruginosa* at times of upper respiratory infections at the first sign of an increase in symptoms and signs of their chest infection.
- These patients will usually be taking a regular nebulised anti-pseudomonal antibiotic, which should be continued.

4.8 Use of chloramphenicol

4.8.1 Introduction

Chloramphenicol has *in vitro* activity against *H. influenzae* and *P. aeruginosa*. There are anecdotal reports of a clinical response in patients with *P. aeruginosa* and *B. cepacia* complex. Recently it has become very expensive to prescribe. There are concerns about the very rare side-effect of aplastic anaemia (www.medicines.org.uk). Since there are many antibiotics effective against *H. influenzae*, it should rarely be used to treat infection with this organism. There is only anecdotal evidence in favour of the use of chloramphenicol in infection with *P. aeruginosa*, but some clinicians find it to be an effective orally active agent in this context. There seems little advantage to intravenous chloramphenicol compared with other intravenous anti-pseudomonal antibiotics in most cases. There is no consensus or evidence base on which to base recommendations about frequency of monitoring full blood counts during chloramphenicol therapy. We can find no report of this complication in a CF patient.

4.8.2 Recommendations for use of oral chloramphenicol

- The use of oral chloramphenicol in patients chronically infected with *P. aeruginosa*, with a mild to moderate exacerbation of respiratory symptoms, has been anecdotally associated with improvement in small numbers of patients. Where there are few alternative antibiotics, due to the resistance pattern of the organism, a trial of chloramphenicol may be justified. The patient should be fully informed of the risks of chloramphenicol.

4.9 Risks of oral antibiotics

Generally, oral antibiotics have been very beneficial in CF. The risks include allergic reactions, staining of the teeth (co-amoxiclav in liquid form and tetracyclines in children under 12 years) and secondary infection with *Clostridium difficile*. One study showed that 14/30 asymptomatic CF patients had stools positive for *Clostridium difficile*. There was no difference between the positive and negative
groups in terms of the chronic use of oral antibiotics. Hence, isolation of this organism may not always be of pathological significance. As in all therapeutic decisions, the risks and benefits of oral antibiotics should be weighed on an individual basis.

4.10 Macrolides in CF

4.10.1 Introduction

Long-term use of some macrolides such as azithromycin appear to have beneficial effects in patients with CF and P. aeruginosa.16–20 [1+] The mode of beneficial action is not known. In a prospective randomised double blind placebo controlled study of azithromycin 250 mg daily for 3 months in adults with CF, the azithromycin treated patients had stable respiratory function, reduced mean C-reactive protein levels, fewer courses of intravenous antibiotics and improved quality of life scores.20 [1+] A double blind randomised controlled crossover trial of 6 months azithromycin 250 mg (<40 kg) or 500 mg (>40 kg) daily or placebo in children more than 8 years old and with FEV1 <80%, showed significant benefit while azithromycin was being taken.16 In a multicenter, randomized, double-blind, placebo-controlled trial patients who were aged 6 and over, with FEV1 > 30% predicted, received either azithromycin (n = 87) 250 mg (weight <40 kg) or 500 mg (weight > or =40 kg) of oral azithromycin 3 days a week for 168 days or placebo. The azithromycin group had significant improvements in FEV1 and body weight, and reduced rates of infective exacerbations.19 [1+] A beneficial effect on infective exacerbations was seen even in patients who did not have an improvement in lung function. There is some evidence that beneficial responses to azithromycin correlate with in vitro effects on P. aeruginosa.21 Some clinicians are now using long-term azithromycin in patients chronically infected with P. aeruginosa when their progress is unsatisfactory. Benefit is also seen in non-Pseudomonas infected patients. A multicentre, randomised, double blind, placebo controlled in children age > 6 years with FEV1 > 40% compared either 250 mg or 500 mg (body weight < or > 40 kg) of oral azithromycin three times a week for 12 months.22 [1+] There was no change in lung function, but the number of pulmonary exacerbations, the time elapsed before the first pulmonary exacerbation, and the number of additional courses of oral antibiotics were significantly reduced in the azithromycin group regardless of infection with P. aeruginosa. The Cochrane review concluded that there was clear evidence of a small but significant improvement in respiratory function following treatment with azithromycin, but that further studies were needed to clarify the precise role of azithromycin in the treatment of CF lung disease.23 [1++] A single study comparing once weekly with once daily azithromycin showed equivalence for most outcomes, but daily dosing giving better nutritional outcomes for children and fewer gastrointestinal side-effects for all ages. Further work is needed before daily therapy can be recommended.24 [1+]

4.10.2 Recommendations for use of oral macrolides (section 8.10)

- **Macrolides are definitely beneficial in some patients with CF [A].**

- **A six month trial of oral azithromycin should be considered in patients who are deteriorating on conventional therapy, irrespective of their infection status. Not all patients will benefit from this therapy. The dose should be: 10 mg/kg/dose if body weight <15 kg; 250 mg if < 40 kg; 500 mg if > 40 kg, dose frequency three times per week [A]. Azithromycin is not licensed in children under 6 months of age.**

- **Although there is anecdotal evidence that adding azithromycin to the regimen of all those chronically infected with P. aeruginosa is beneficial,25,26 there is insufficient evidence to recommend this [D].**
4.11 References


5. NEBULISED ANTIBIOTICS

5.1 Introduction

People with CF and chronic *Pseudomonas aeruginosa* infection have a worse prognosis than those with occasional or no *P. aeruginosa* infection. \[2+\] Chronic infection accelerates the progressive decline in pulmonary function characteristic of CF and is central to the respiratory related morbidity and mortality.

Regular courses of intravenous antibiotics have improved survival by reducing sputum bacterial load and maintaining pulmonary function but they interfere with daily living and increase the risk of antibiotic hypersensitivity reactions and adverse drug effects. \[2-\]

The advantages of nebulised antibiotic therapy for pseudomonas infection in CF have been recognised for over 30 years. \[3\] The hypothesis is that an antibiotic delivered directly to the site of infection will be maximally effective. As the ionic environment in the CF lung may reduce drug accumulation by the bacteria, and aminoglycoside efficacy may be reduced by binding to the excess extracellular neutrophil DNA, \[4\] it has been suggested that sputum concentrations 25 times greater than the MIC are necessary to achieve a bactericidal effect. \[5\] These levels cannot be reached by intravenous administration without unacceptable risks of systemic toxicity but can be realised by inhalation of aerosolised antibiotics, which because of their minimal systemic absorption are unlikely to cause ototoxicity or nephrotoxicity. \[6\] Although the concentration of aerosolised antibiotic in bronchial secretions may not always achieve bactericidal levels with the currently used doses and in the presence of pulmonary abscesses, sublethal concentrations may diminish bacterial virulence factors. \[7\] The degree of lung damage does not appear to affect total pulmonary antibiotic deposition, although with more severe disease less inhaled antibiotic reaches the lung periphery. \[8\]

5.2 Delay or prevention of chronic infection with *P. aeruginosa*

5.2.1 Introduction

Strategies aimed at preventing or delaying progression from initial acquisition of *P. aeruginosa* to chronic infection are central to the management of patients with CF. Early eradication therapy and the subsequent reduction in the prevalence of chronic *P. aeruginosa* infection is a major reason for increased patient survival. \[9\; 10\] \[2-\] Recent data suggest that the window of opportunity for pseudomonas eradication strategies may be quite large. \[11\] Chronic infection is usually associated with the mucoid variant. Whilst acquisition of *P. aeruginosa* may occur quite early in life, the transition from the non-mucoid to the mucoid phenotype may take several years.

Early administration of aerosolized antibiotics once infection with *P. aeruginosa* has been identified significantly reduces the risk of chronic infection. \[12\; 15\] \[1+\] The study by Valerius *et al* documented the efficacy of early treatment with oral ciprofloxacin and aerosolized colistin twice daily for three weeks. \[11\] \[1+\] Further experience showed more effective eradication of *P. aeruginosa* when the duration of treatment was increased to three months and the frequency of nebulised colistin dosage to thrice daily. After three-and-a-half years only 16% of treated patients had developed chronic *P. aeruginosa* infection in comparison to 72% of untreated historical controls (p < 0.005). \[16\] \[2-\] A subsequent study has shown effective eradication of early infection with tobramycin solution for inhalation (TSI) 300 mg twice daily for 28 days. \[14\] There are no studies comparing the above regimens with each other, and in particular no study comparing colistin with TSI. A Cochrane systematic review, which included only well designed randomised controlled trials, concluded that there was evidence for short term eradication with a number of eradication regimens. \[17\] \[1++\] Individual clinics vary in the
protocols adopted. An initial treatment protocol combining nebulised colistin with oral ciprofloxacin for 3 months is widely used. A step wise regimen, as described by Fredericksen et al can also be used. Nebulised TSI should be reserved for early relapse and for patients intolerant of inhaled colistin.

When patients present with a new pseudomonas isolate associated with a respiratory exacerbation, however mild, a two week course of intravenous anti-pseudomonal antibiotics should be considered before starting treatment with nebulised colistin and oral ciprofloxacin. Centres with access to pseudomonas antibody measurements may wish to consider prescribing an eradication protocol for patients showing a rise in antibody levels even when *P. aeruginosa* is not cultured from respiratory samples. Eradication therapy is usually well-tolerated. Absorption of TSI does not reach sufficient levels in the majority of patients to affect renal function but clinicians should be cautious.

There has been no evidence to suggest significant increases in antimicrobial resistance during eradication therapy, even after multiple repeat courses. The use of nebulised antibiotics is associated with culture of *Aspergillus* sp.

### 5.2.2 Recommendations for eradication of *P. aeruginosa* when detected in respiratory secretions (section 8.7)

- **First line therapy should be based on a regimen of nebulised colistin and oral ciprofloxacin. Many centres will use 3 months of treatment from the outset. An alternative is to use a 3 step regimen, as described by Frederiksen et al.**

- **Patients presenting with a new growth of *P. aeruginosa* and a respiratory exacerbation may receive two weeks of intravenous anti-pseudomonal antibiotics before commencing nebulised colistin and oral ciprofloxacin.**

- **TSI should be considered for patients showing early regrowth of *P. aeruginosa* and for those intolerant of colistin or ciprofloxacin.**

- **If in extenuating circumstances the physician wishes to administer a more prolonged course of inhaled antibiotic, it is recommended that nebulised antibiotic treatment is withdrawn after a year of negative *P. aeruginosa* cultures.**

### 5.3 Prevention of clinical deterioration in patients chronically infected with *P. aeruginosa*

#### 5.3.1 Introduction

Regular nebulised antibiotics reduce the rate of deterioration of respiratory function in patients chronically infected with *P. aeruginosa*. In 1981 Hodson et al compared six months of treatment with twice-daily nebulised gentamicin (80 mg) and carbenicillin (1 g) against placebo. In the active arm patients showed significantly improved respiratory function and a non-significant trend towards fewer hospital admissions. Initial follow-up studies were methodologically poor but demonstrated the potential benefits of nebulised antibiotic therapy for chronic *P. aeruginosa* infection: improved lung function, a slower decline in lung function, fewer hospital admissions, better clinical scores and weight, and decreased *P. aeruginosa* density and virulence factors. There was no renal toxicity, ototoxicity, or increase in bacterial resistance.
Nebulised colistin achieves low systemic and high local concentrations in the lung, supporting its use in patients with *P. aeruginosa* infection. In 1999 the publication of a randomised, double blind study of nebulised TSI provided evidence for the benefits of nebulised antibiotic treatment in the management of chronic *P. aeruginosa* infection. Patients in the active arm received three cycles of 300 mg tobramycin solution for inhalation (TSI). Each cycle consisted of 28 days treatment followed by 28 days off treatment. The first cycle of treatment produced a 12% increase in FEV1 which was maintained through the study. In the active arm there was a significant fall in colony forming units per gram of sputum, and patients required fewer intravenous antibiotic treatments. Sputum drug concentrations more than 25 times the MIC value were seen in 95% of patients. Adolescent patients responded particularly well with 14% improvement in FEV1 compared with 1.8% for controls. The long term safety and efficacy of TSI was assessed in a 96 week study. There were no significant adverse events, or increased isolation of intrinsically tobramycin resistant micro-organisms. Treated patients had fewer hospital admissions and intravenous antibiotic use, and better preservation of respiratory function.

A comparative study of twice-daily TSI (300 mg) and nebulised colistin (1 mega unit), at present the only antibiotics licensed in the UK for nebulisation in cystic fibrosis, showed that both treatments reduced the bacterial content of the sputum significantly and increased FEV1 by 6.7% and 0.37% respectively. In this short term study there were no new growths of *S. maltophilia* or *Burkholderia cepacia* complex and no significant increase in bacterial resistance.

A Cochrane Review found insufficient evidence to claim superiority for either TSI or colistin. Eleven trials met the inclusion criteria. The review concluded that nebulised antibiotic treatment improves lung function and reduces the frequency of respiratory exacerbations. There was no evidence of clinically important adverse events.

### 5.3.2 Recommendations for patients chronically infected with *P. aeruginosa* (section 8.9)

- **Patients with chronic *P. aeruginosa* infection should be considered for regular nebulised anti-pseudomonal antibiotic treatment [A].**
- **Initial treatment should be with nebulised colistin [D].**
- **If colistin is not tolerated or if clinical progress is unsatisfactory, TSI should be used at a dose of 300 mg twice daily for 28 days followed by 28 days off treatment and then repeat. (TSI should be administered 12 hourly. If a shorter interval between morning and evening doses is needed for practical reasons, then the interval should not be less than 6 hours) [C].**

### 5.4 Nebulised antibiotics in acute respiratory exacerbations

There is no evidence that nebulised antibiotics are suitable alternatives to intravenous antibiotics for infective exacerbations, or that there is clinical benefit when nebulised antibiotics are used as an adjunct to intravenous antibiotics for the treatment of respiratory exacerbations. Nonetheless, some centres are using TSI for the treatment of acute respiratory exacerbations because of the high endobronchial antibiotic levels achieved. TSI may be useful in the treatment of exacerbations associated with multi-resistant *P. aeruginosa*. The high sputum drug concentrations may render the usual laboratory breakpoints meaningless.
5.5 Nebulised antibiotics to prevent *Paeruginosa* infection

Twice daily inhaled gentamicin in a small group of very young children appeared to prevent chronic infection for a mean of 78 months. Nebulised TSI, colistin, injectable forms of tobramycin, or amikacin may have been important in achieving a chronic *Paeruginosa* infection rate of <3% in Belgian children. Potential advantages of this proactive approach need to be set against the increased risks of encouraging bacterial resistance and the emergence of fungal organisms, the potential toxicity of treatment, the ability to prevent chronic *Paeruginosa* infection in the majority of children with less invasive protocols, and the impact on daily life of long term nebulised antibiotic treatments.

5.6 Nebulised antibiotics in the treatment of non-tuberculous mycobacterial infection

Non-tuberculous mycobacteria (NTM) are environmental organisms found in soil, dust, and water systems. The increasing prevalence of NTM infection in CF is probably a consequence of more successful treatment of the usual CF pathogens. For a full discussion of the diagnosis and management of NTM infection in CF (section 7.8), Nebulised amikacin is recommended as part of maintenance treatment for infection with one form of NTM – *Mycobacterium abscessus*. Full recommendations are given in section 7.8.3. There is no evidence base for dosage but 500 mg bd is recommended. This may need reducing to 250 mg bd in younger children. The injectable preparation (250 mg/ml) should be used and made up to 4 ml with 0.9% sodium chloride (for standard nebuliser/compressor systems).

5.7 Nebulised amphotericin in the treatment of allergic bronchopulmonary aspergillosis (ABPA)

5.7.1 Introduction

*Aspergillus fumigatus* can act as an allergen and induce a hypersensitivity reaction in the lungs of patients with CF known as allergic bronchopulmonary aspergillosis (ABPA). This is often associated with increased respiratory symptoms due to wheeze, mucus plugging and non specific infiltrates, and reduced lung function. ABPA often responds well to oral prednisolone but corticosteroid use increases the risk of diabetes mellitus, osteoporosis and impaired growth. These risks may be partly offset by using antifungal therapy. Itraconazole may allow lower steroid doses in the treatment of ABPA but is poorly absorbed when given orally to persons with CF. Voriconazole has greater bioavailability than itraconazole but is more expensive and has a significant number of interactions with other drugs. Nebulised antifungal agents such as amphotericin B may be considered when response to conventional therapy is poor.

5.7.2 Recommendations for nebulised anti-fungals in patients with ABPA

- **Amphotericin or liposomal Amphotericin (Ambisome®, Gilead, Cambridge UK)** should be prescribed at a dose of 25 mg bd. Reconstitution and administration is as follows (D):
  - Conventional amphotericin: 50 mg dissolved in 8 ml of water for injection and 4 ml (25 mg) used.
  - Liposomal amphotericin: A 50 mg vial dissolved in 12 ml of sterile water and 6 ml (25 mg) used.

Liposomal preparations are expensive and there is no evidence base for their superior efficacy. Patients should be monitored for bronchospasm.
5.8 Nebulised taurolidine for the treatment of *Burkholderia cepacia* complex infection (section 8.13)

Taurolidine is an antibiotic and an antiendotoxin with a broad spectrum of activity against gram-negative and positive bacteria and fungi. It is an unlicensed product available as an intraperitoneal lavage (250 ml) and line lock (5 ml) (Taurolin®/Taurolock®, Geistlich Pharma AG, Zurich, Switzerland). In people with CF *in vitro* data confirm the activity of taurolidine against *P. aeruginosa* and *Burkholderia cepacia* complex (Bcc) but a randomised double blind placebo controlled trial of 4 ml nebulised taurolidine solution 2% vs. sodium chloride solution in 20 adult patients with CF showed no in vivo anti-Bcc activity. There were no changes in Bcc colony counts or spirometry over four weeks treatment. Successful Bcc eradication has been reported, temporarily, in a non-CF patient. Taurolidine may cause bronchospasm, cough or a mild ‘burning’ sensation in the throat. An initial test dose should be given. Care is advised in renal insufficiency.

5.9 Recommendations for nebulised vancomycin for the treatment of MRSA

- Nebulised vancomycin has been used as part of treatment protocols for the eradication of MRSA in patients with CF but there are no trials comparing one regimen with another. Five days treatment with nebulised vancomycin may be used as part of an eradication protocol [D]. Dosage:
  - Adults: 250 mg bd or qds (200 mg/4 ml sterile water or 0.9% sodium chloride can be used for acceptable nebulisation time – for standard nebuliser/compressor systems).
  - Children: 4 mg/kg (max 250 mg) in 4 ml sterile water or 0.9% sodium chloride bd or qds – for standard nebuliser/compressor systems.

In adults and children nebulised vancomycin should be preceded by an inhaled bronchodilator.

5.10 Assessment and administration

5.10.1 Introduction

Patients should be carefully assessed before and after a treatment with nebulised antibiotics by spirometry and chest auscultation. Studies in both children and adults have established that bronchoconstriction occurs following inhalation of antibiotics and this may be prevented by bronchodilator inhalation given before the antibiotic. Cumulative tightness has been reported despite no evidence at the test dose and clinicians should be attentive to this in follow up monitoring.

A mouthpiece is preferable to a mask to maximise pulmonary deposition, although small children below 3 years will usually require a mask held firmly on the face.

Breathing patterns influence pulmonary deposition. Relaxed tidal breathing through the mouth, not the nose, improves deposition. A nose clip will therefore increase the efficiency of delivery to the lungs when inhaling from a device delivering continuous nebulisation. Adaptive aerosol delivery devices (AAD) deliver a preset and precise repeatable dose irrespective of nose or mouth breathing however a nose clip will shorten treatment times for those patients where this a problem. Electronically controlled inhalations have shown greater and more peripheral deposition than conventional inhalation even when the patients were experienced with inhalation therapy and were supervised by a physiotherapist.
5.10.2 Recommendations for administration of nebulised antimicrobials

- The first dose should be administered in hospital and bronchoconstriction excluded by pre and post inhalation spirometry where possible and by chest auscultation for all patients. Follow up should exclude cumulative tightness [C].

- Bronchoconstriction usually occurs immediately after nebulised antibiotic administration and may be prevented by pre dose bronchodilator inhalation [C].

- Nebulised antibiotics should be taken after airway clearance to ensure maximum deposition [C].

- A mouthpiece is preferable to a facemask to maximise pulmonary deposition [C].

- Children below 3 years of age will usually require a mask held firmly on the face but inhalation will be ineffective if the child is crying [C].

- The new generation nebuliser systems e.g. eFlow® rapid (Pari Medical, West Byfleet, UK) and I-neb® (Respironics, Chichester, UK) are preferred by many patients [D].

- Breathing patterns should be observed and corrected if inhaling from a device delivering continuous nebulisation. Computer software e.g. I-neb® Insight AAD® System, (Respironics, Chichester UK) gives visual feedback and aids training for the I-neb® [D].

- Adherence to treatment should be checked subjectively after a period of home use. Irregular usage is not recommended and is a reason for stopping treatment. The I-neb® Insight AAD® System objectively monitors the delivered dose to allow clinicians to work with patients to improve adherence [D].

5.11 Antibiotic choice and formulation

At the time of writing, Colistin and TSI are the only antibiotics licensed in the UK for inhalation. Other antibiotics should not usually be prescribed for P. aeruginosa infection. The injectable tobramycin preparation should not be used.

5.12 Safety of long term inhaled antibiotics

5.12.1 Increased bacterial resistance

TSI is associated with increasing P. aeruginosa tobramycin resistance as documented by standard laboratory tests.60 This does not appear to diminish its efficacy, although future widespread resistance to intravenous tobramycin may be a major clinical problem. Resistance patterns should be monitored. Colistin resistance is rare.61

5.12.2 Intrinsically resistant bacteria

There is no conclusive evidence that the use of nebulised antibiotics increases the prevalence of infection with B. cepacia complex, Achromobacter xylosoxidans, or S. maltophilia.

5.12.3 Serum aminoglycoside concentrations

Clinicians should consider the possibility of toxic drug levels resulting from nebulised antibiotic delivery, especially if used in conjunction with intravenous administration of the same antibiotic. A retrospective review of children with CF receiving inhaled gentamicin showed significantly raised
urinary N-acetyl-ß-D-glucosaminidase (NAG) activity (which is an indicator of renal tubular damage) compared to control children who had never received inhaled gentamicin or who had discontinued the drug at least three months previously. There was a positive correlation between NAG levels and cumulative antibiotic dose.\textsuperscript{62} The long term clinical implication of these findings are uncertain as urinary NAG activity returned to normal at the end of treatment.

Acute renal failure has been reported after one week of nebulised TSI and concurrent ciprofloxacin. Serum tobramycin levels 24 hours after the last inhaled dose and the renal biopsy picture were consistent with aminoglycoside induced damage.\textsuperscript{63} Reversible vestibular dysfunction has been reported with TSI in a non-CF patient with pre-existing renal insufficiency.\textsuperscript{64}

Patients show a range of systemic absorption probably reflecting individual differences that the treating physician cannot predict. Systemic absorption may be greater with the more efficient antibiotic delivery achieved by the I-neb\textsuperscript{®} and eFlow\textsuperscript{®} rapid. \textit{(section 5.16)}

\textbf{5.12.4 Bronchoconstriction}

The respiratory side effects of aerosolised antibiotics are mainly limited to bronchoconstriction at time of delivery. This should be actively looked for before prescribing long term treatment. Patients may respond to concurrent or predose bronchodilators.\textsuperscript{65–67}

\textbf{5.12.5 Pregnancy}

Tobramycin crosses the placenta and accumulates in the amniotic fluid, fetal plasma and in the kidneys. Its use in pregnancy has not been linked to congenital defects but there is a theoretical risk of damage to the VIII cranial nerve and of nephrotoxicity. Avoidance of parenteral administration is recommended during pregnancy.

The risks from nebulised administration are much less. A decision whether or not to continue nebulised antibiotic treatment during pregnancy should be made on an individual basis and in consultation with the patient. The minimal but theoretical risks to the baby of continued treatment should be weighed against the risks to the mother’s health of stopping treatment.

\textbf{5.12.6 Nebuliser equipment as a source of bacterial contamination}

Nebulisers may act as a source of bacterial contamination.\textsuperscript{68,69} Incorrect care of a nebuliser/compressor system may also result in inefficient drug delivery.

\textbf{5.12.7 Other}

Cutaneous rashes are rare but may occur with nebulised drugs. A sore mouth may be due to \textit{Candida albicans} infection.

\textbf{5.12.8 Recommendations to minimise systemic adverse effects}

\begin{itemize}
  \item \textit{Clinicians should be aware of the potential for systemic absorption and toxic antibiotic effects [D].}
  \item \textit{Nebulised antibiotic administration should usually be suspended during intravenous antibiotic treatment. For patients with renal impairment TSI may be preferred to the parenteral route for acute exacerbations but there is little direct evidence of efficacy. Nebulised colistin may be continued for the treatment of multiresistant infection [D].}
\end{itemize}
• If a facemask is used the face should be washed after nebulisation [D].

• The pros and cons of continuing nebulised antibiotic treatment during pregnancy should be individually assessed [D].

5.12.9 Recommendations on nebuliser maintenance

• Patients should be instructed to carefully follow manufacturers instructions for cleaning nebulisers [D].

• An electrical compressor should have an inlet filter, which should be changed according to manufacturers instructions [D].

• Hospitals issuing nebuliser/compressor systems should arrange for their regular servicing. Patients who have purchased their own nebuliser/compressor systems should have their equipment serviced by the hospital where they attend for their CF care. The I-neb® is the property of the manufacturer. Repairs and replacement consumables are dealt with directly between the patient and company [D].

5.13 Environmental safety

5.13.1 Introduction

There is no published evidence to support or refute concern that nebulised antibiotics may be a health hazard to medical personnel or the hospital and home environment. It has been suggested that aerosolised antibiotics may encourage the emergence of resistant organisms, particularly on intensive care units. Patients, however, usually stop nebulised antibiotic treatment when receiving intravenous antibiotics in hospital. At home, patients should nebulise their antibiotics in a separate room. They do not need to filter their exhaled antibiotics for safety reasons, although they may wish to do so to eliminate the odour and protect surrounding furniture from sticky deposits. If for practical reasons it is not possible to nebulise in a separate room filters are recommended.

5.13.2 Recommendations on environmental safety

• In hospital the local Trust policy should be followed [D].

• In hospital, a nebuliser should be fitted with a high efficiency breathing filter on the expiratory port, to prevent environmental contamination. For I-neb® (section 5.16) [D].

• It is advisable for patients to receive nebulised antibiotics in a separate area from other patients [D].

• If the patient has a sibling with cystic fibrosis the use of a filter is mandatory [D].

• Mothers with CF who have young children should use a filter when nebulising antibiotics [D].
5.14 Antibiotic delivery

5.14.1 Antibiotic preparations

Colistin is dispensed as a dry powder preparation and reconstituted as a solution using 0.9% sodium chloride, Water for Injections or a 50:50 mixture to a volume of 4 ml for continuous nebulisation, (2.5 ml for a low residual volume nebuliser). Chest tightness is a known side effect of the drug and this may be minimised by altering the tonicity of the solution. The I-neb® requires a volume of 1 ml and should be used with the Promixin® brand of colistin.

Reconstituting colistin with a bronchodilator is an emerging practice to shorten treatment times. It is recommended that admixtures should be prepared immediately before use, with preservative free diluents and both the physico-chemical compatibility and aerodynamic properties of the mixtures should be considered.

5.14.2 Recommendations for reconstitution of nebulised antimicrobials

- Colistin should be reconstituted to an isotonic or hypotonic solution.
- To prepare an isotonic solution of Colomycin® suitable for nebulisation in adults: 2MU in 4.0 ml -> add 2.0 ml water for injections + 2 ml of 0.9% sodium chloride.
- To prepare an isotonic solution of Colomycin® suitable for nebulisation in children: 1MU + 1 ml water for injections + 1 ml 0.9% sodium chloride. (For children over 10 years the 2MU dose may be more suitable – see section 5.15 below).
- TSI is dispensed as a ready to use solution in a 300 mg/5 ml vial.
- Colistin should be reconstituted immediately before use.
- A supervised test dose should be performed with measurement of spirometry before and after inhalation.
- Any induced bronchoconstriction may be prevented by preceding the inhalation with a bronchodilator.

5.15 Antibiotic doses

There is no evidence base for the dose of colistin. The licensed doses are as follows:

Children <2 years: 500,000–1 million units bd
Children>2 years and adults: 1–2 million units bd

Many CF centres use 1MU bd for children <2–10 years and 2MU bd for patients over 10 years.

For the I-neb®, 1MU is reduced to 0.5MU and 2MU reduced to 1MU of Promixin®, due to the increased efficiency of drug delivery.

TSI is administered as a 300 mg dose bd for 28 days every alternate four week period.
5.16 Nebuliser/compressor systems for antibiotics

5.16.1 Characteristics of available devices

Delivery devices for antibiotics are divided into the traditional conventional nebuliser/compressor systems and the more recent devices which utilise vibrating mesh technology. Conventional systems consist of a jet nebuliser and electrical air compressor.

The new generation of nebulisers has advanced from jet nebulisation to vibrating mesh technology which produces a fine, dense aerosol cloud of low velocity e.g. eFlow® rapid and I-neb®. They provide shorter treatment times with improved efficiency and efficacy of deposition. These devices are small, light weight, silent and battery driven.

The I-neb® has the additional features of AAD® and ‘target inhalation mode’ (TIM). AAD® adapts to the individual’s breathing pattern and targets antibiotic delivery to the first part of inspiration. A predetermined dose is delivered with audible feedback on successful completion. Drug delivery is therefore precise and reproducible with each administration. No drug is delivered during expiration and environmental contamination is eliminated. (1% of exhaled fraction during tidal breathing mode and 0.2% during TIM).73 TIM promotes a slow deep inhalation which is controlled by restricting the inspiratory flow to 15 L/min. Sensory feedback to the lip indicates the expiratory phase. This mode of inhalation results in high peripheral deposition74 and is acceptable to patients.75

An RCT of an earlier device, utilising AAD® (Halolite®), compared the use of the AAD and conventional high output nebuliser system in 259 patients with CF in a multicentre trial. The AAD was preferred by patients, increased their adherence to treatment and resulted in more doses being taken to an acceptable level. It was suggested that the increased chest tightness observed after inhalation of colistin using the AAD might have been due to more successful delivery to the lungs.76;77 The use of bronchodilator solution in patients using AAD with colistin had a positive effect on maintaining both short and long-term FEV1, as opposed to bronchodilator via a metered dose inhaler or dry powder inhaler.76 In another study, using the AAD system, colistin in doses up to 2MU dissolved in 2 ml of 0.9% sodium chloride was well tolerated.78

Studies evaluating AAD® and I-neb® have demonstrated increased pulmonary deposition compared to conventional systems.78-80 Whilst it is recognised that conventional systems may under-dose patients, clinicians should be attentive to the potential for over-dosing with the new devices. Individual patient monitoring and follow up is recommended.

The eFlow® rapid delivers continuous nebulisation with exhaled antibiotic into the environment. Any requirement for filtering would apply to this device. Audible cut out occurs at the end of treatment based on the remaining residual volume of the nebuliser. Drug delivery is angle dependent and accounts for variability of dose delivered.

I-neb® is only available with a prescription of Promixin® and is supplied at no cost by the company. The eFlow® rapid is available for purchase.

5.16.2 Recommendations for nebuliser devices

- For conventional systems use an active venturi nebuliser (breath assisted) e.g. Ventsstream (Respironics, Chichester, UK) or Pari LC Sprint or Pari LC Sprint Star (Pari Medical, West Byfleet UK) with a compressor producing a flow rate of 6 litres per minute. If unacceptably long, the nebulisation time can be reduced for patients with low inspiratory flow [D].

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• The Pari LC Sprint (previously Pari LC plus) is recommended for the administration of TSI [A].
• Refer to manufacturers’ data for recommendations of antibiotic usage and dosage in the I-neb® and eFlow® rapid [D].
• Patients using the new devices should be carefully monitored [D].

5.17 Travel nebuliser/compressor systems

The battery operated lightweight features of the eFlow® rapid and I-neb® make them ideally suited for travel. Other systems include the Freeway® elite (Respironics Chichester, UK).

5.18 References


76. Dodd ME, Conway SP, Marsden RJ, Paul EA, Weller PH. Interaction between bronchodilators and nebuliser device in cystic fibrosis patients taking colistin using a Halolite adaptive aerosol device (AAD) system compared to a high output conventional nebuliser system. European Cystic Fibrosis Society Meeting, Genoa 2002.


6. INTRAVENOUS ANTIBIOTICS

6.1 Introduction

There are 5 key questions in the use of intravenous antibiotics in cystic fibrosis (CF) patients and these will be covered in turn in this section.

- Why treat?
- Who should be treated?
- Which antibiotics should be used?
- What dose, for how long and in what setting should antibiotics be given?
- How can we minimise the cumulative side effects of treatment?

6.2 Why treat?

6.2.1 Early onset of infection and inflammation in CF

In CF, lower respiratory infection begins in the first weeks of life: bronchoalveolar lavage showed the presence of *Staphylococcus aureus* in approximately one third of infants at a mean age of 3 months. A similar study in older children (mean age 17 months) found *S. aureus* in 47%, *Haemophilus influenzae* in 15% and *Pseudomonas aeruginosa* in 13%. Lower respiratory infection in young children with CF is associated with more frequent wheezing, increased levels of inflammatory mediators, and air trapping. When infection is successfully treated, inflammatory mediators fall to pre-treatment levels. It has been suggested that the presence of pathogenic organisms in the lower respiratory tract sets up a vicious cycle of infection, inflammation and lung damage which leads to bronchiectasis and ultimately, respiratory failure and death. Although there is some evidence that the CF genotype itself may promote inflammation, there is no doubt that the early treatment of infection is crucial in delaying or halting the inflammatory cycle.

6.2.2 *Pseudomonas aeruginosa*

Most CF patients in the UK have developed chronic pulmonary infection with *P. aeruginosa* by their late teens, and this is associated with a more rapid decline in lung function and increased mortality. The organism has innate resistance to many antibiotics, and furthermore it can elude the host immune system and the action of antibiotics by forming complex colonies, known as biofilms, on damaged respiratory epithelium. In young patients with CF there is genetic heterogeneity in isolates of *P. aeruginosa* suggesting repeated new infections, but in adults with chronic *P. aeruginosa* infection, pulmonary exacerbations are usually not caused by a new strain. However, sensitivity patterns may change from when the patient is stable to when they have an exacerbation. Antibiotic therapy may be selected on the basis of the last available sputum or cough swab result but should be amended when the culture and sensitivities are available from a sample taken during the exacerbation, if the patient’s clinical response is poor. Whilst the laboratory report of antibiotic susceptibility is a guide, this will not always correlate with clinical response.

6.2.3 Evidence for the use of intravenous antibiotics

Although intravenous antibiotics have played a central role in the management of pulmonary infection in CF patients for 4 decades, there have only been two studies comparing their action against a placebo. Both were small (less than 20 patients in each arm) and underpowered. In the earlier of the two (Wientzen *et al.*) there were two deaths and more patients with a poor clinical outcome in the placebo group. In the later study of Gold *et al.* there was no difference in clinical outcomes.
outcome between active and placebo groups, but a quarter of the patients receiving placebo elected to withdraw from the study in order to have antibiotics. Nevertheless, the weight of clinical experience indicates that patients with exacerbations of chronic pulmonary infection with *P. aeruginosa* benefit from antibiotic therapy.\textsuperscript{13}

The use of regular prophylactic intravenous antibiotics (given every 3 months) in CF patients chronically infected with *P. aeruginosa* is more debatable. Although it was suggested as one of the most important factors in the excellent survival seen in Danish CF patients,\textsuperscript{14} a randomised controlled trial of regular 3 monthly intravenous antibiotics vs. intravenous treatment given only for exacerbations of pulmonary symptoms showed no difference in lung function between the two groups.\textsuperscript{15} This study was underpowered, and there appeared to be convergence of the two therapeutic strategies, with a mean of 3 courses of intravenous antibiotics given per year in the symptomatic treatment group vs. 4 per year in the elective group.

There are many other important lower respiratory pathogens affecting CF patients, including *Staphylococcus aureus*, Meticillin-resistant *S. aureus* (MRSA), *H. influenzae*, *Burkholderia cepacia* complex, other gram-negative organisms and atypical mycobacteria. The treatment of many of these organisms is described in section 7.

### 6.3 Who should be treated?

Patients with a pulmonary exacerbation should be treated with extra antibiotics, in addition to any they may be using for prophylaxis (section 4). However, such exacerbations are poorly defined and the only validated definitions have been designed for research purposes.\textsuperscript{16-18} In clinical practice, most physicians will look at a number of parameters:

- Increased productive cough or breathlessness
- Decreased exercise tolerance
- Loss of appetite
- Absence from school or work
- Changes in the appearance or volume of sputum
- New signs on chest auscultation
- New chest radiographic signs
- Fever
- Fall in respiratory function

The decision to commence intravenous antibiotics should be made jointly by the clinician and the patient or parent. It will depend upon the severity of the exacerbation and the response to previous exacerbations. Important social issues such as work and school commitments, exams and holidays may need to be considered. Persisting low grade symptoms such as cough alone are indication for intravenous antibiotics if other treatment options (such as oral antibiotics) have failed to bring about an improvement.

### 6.4 Which antibiotics should be used?

#### 6.4.1 General principles

This depends on the organism present in the sputum or cough swab or the most recent historical isolate. The sensitivity of the organism as reported by the microbiologist may act as a guide. However the sensitivity pattern (antibiogram) and the clinical response shown by the patient may be discordant, particularly when there is infection with *P. aeruginosa*. The following antibiotics are often used for the
categories of infection listed. First line treatment of *P. aeruginosa* comprises a β-lactam e.g., ceftazidime (section 8.8.2), meropenem (section 8.8.3) or an anti-pseudomonal penicillin (section 8.8.1) combined with tobramycin (section 8.8.5) or colistin (section 8.8.4). Colistin is often reserved for more resistant *P. aeruginosa* but can also be useful where there are specific contraindications to tobramycin (e.g., hearing impairment) or to reduce cumulative exposure to tobramycin. However it is important to appreciate that both tobramycin and colistin can be toxic to the renal tubule.

*P. aeruginosa*: ceftazidime, tobramycin, meropenem, colistin, anti-pseudomonal penicillins (e.g., ticarcillin-clavulanic acid, piperacillin-tazobactam), aztreonam, fosfomycin. Sensitive strains of *S. aureus*: flucloxacillin, sodium fusidate, (may be combined with oral rifampcin).

**MRSA**: teicoplanin, vancomycin.

*Candida albicans (infection of an indwelling intravenous access device)*: fluconazole, amphotericin, caspofungin.

*B. cepacia*: meropenem, temocillin, ceftazidime, co-trimoxazole

The following table gives guidance on antibiotic prescribing and administration (also sections 8.8, 8.11, 8.12 & 8.14). Many clinicians will stop nebulised antibiotics, whilst the patient is receiving intravenous antibiotics.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Age/weight</th>
<th>Dose</th>
<th>Frequency (times daily)</th>
<th>Maximum Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>IV</td>
<td>1 mth–2 yr 2–12 yrs</td>
<td>30 mg/kg 50 mg/kg 2 g</td>
<td>3–4</td>
<td>2 g x 4 daily</td>
<td>2 wk</td>
</tr>
<tr>
<td>(section 8.12)</td>
<td></td>
<td>Over 12 yr &amp; adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin (Doses are for</td>
<td>IV</td>
<td>Test dose</td>
<td>100 micrograms/kg 1 mg/kg/day 1 mg/kg/day 3 mg/kg/day</td>
<td>1 dose</td>
<td>1 mg 5 mg/kg/day</td>
<td>1 dose 2 wk</td>
</tr>
<tr>
<td>“Ambisome” liposomal formu-</td>
<td>(infusion rate varies with preparation)</td>
<td>Start Increase by Ongoing dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>latation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>IV (60 min infusion)</td>
<td>2–18 yr Adult &lt;80 kg</td>
<td>70 mg/m2 loading dose then 50 mg/m2 70 mg loading dose then 50 mg daily 70 mg daily</td>
<td>1</td>
<td>70 mg</td>
<td>2 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult &gt;80 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazidime</td>
<td>IV (30 min infusion)</td>
<td>1 mth–18 yrs</td>
<td>50 mg/kg</td>
<td>3</td>
<td>3 g x 3 daily</td>
<td>2 wk</td>
</tr>
<tr>
<td>Colistin</td>
<td>IV (30 min infusion)</td>
<td>&lt;60 kg</td>
<td>25,000 Units/kg 1–2 million units</td>
<td>3</td>
<td>2 million units x 3 daily</td>
<td>2 wk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;60 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotrimoxazole1</td>
<td>IV (60 min infusion)</td>
<td>6 mths–6 yrs 6–12 yrs 12 yrs</td>
<td>240 mg 480 mg 960 mg</td>
<td>2</td>
<td>2</td>
<td>1.44 g x 2 daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole (for systemic</td>
<td>IV (30 min infusion)</td>
<td>1 mth–18 yrs Adult</td>
<td>6–12 mg/kg 400 mg</td>
<td>1</td>
<td>1</td>
<td>400 mg daily</td>
</tr>
<tr>
<td>candidiasis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 mth–18 yrs Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adult</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>IV (30 min infusion)</td>
<td>1–12 yrs (10–40 kg) &lt;12 yr</td>
<td>100 mg/kg 5 g</td>
<td>3</td>
<td>2</td>
<td>2 g x 3 daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>IV (bolus over 5 min or 15–30 min infusion)</td>
<td>4–18 years Child &gt;50 kg &amp; adult</td>
<td>25–40 mg/kg 1–2 g</td>
<td>3</td>
<td>2</td>
<td>2 g x 3 daily</td>
</tr>
<tr>
<td>Piperacillin – Tazobactam2</td>
<td>IV injection over 3–5 mins or infusion over 20–30 mins</td>
<td>&lt;12 yr 12 yr</td>
<td>90 mg/kg 4.5 g</td>
<td>3–4</td>
<td>3–4</td>
<td>4.5 g x 4 daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>IV (bolus or 30 min infusion)</td>
<td>Loading dose Continue on</td>
<td>10 mg/kg 10 mg/kg</td>
<td>2</td>
<td>1</td>
<td>400 mg per dose initially. Check levels to optimise dose. x3 doses</td>
</tr>
<tr>
<td>Ticarcillin – Clavulanic acid3</td>
<td>IV (30–40 min infusion)</td>
<td>1mth–18 yrs Adult</td>
<td>80–100 mg/kg 3.2 g</td>
<td>3–4</td>
<td>3–4</td>
<td>3.2 g x 4 daily</td>
</tr>
<tr>
<td>Tobramycin (needs trough level)4</td>
<td>IV (30 min infusion)</td>
<td>1mth–18 yrs 1mth–18 yrs</td>
<td>10 mg/kg 3.3 g/kg</td>
<td>1</td>
<td>3</td>
<td>Max starting dose 660 mg Max starting dose 220 mg x3 daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Needs peak &amp; trough level2</td>
<td></td>
<td></td>
<td></td>
<td>2 wk</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>IV (Infuse no faster than 10 mg/min)</td>
<td>1 mth–18 yrs &gt;18yr</td>
<td>15 mg/kg 1 g</td>
<td>3</td>
<td>2</td>
<td>Children 666 mg x3 daily Adults 1 g x2 daily</td>
</tr>
</tbody>
</table>

1. Use appropriate dilution (section 8.12). 2. 2.25 g vial = piperacillin 2 g and tazobactam 250 mg
2. 3.2 g vial = ticarcillin 3 g and clavulanic acid 200 mg (section 8.8.1). 4. Trough level before the 2nd & 8th dose (section 8.8.5)
5. Peak & trough levels at 3rd or 4th dose & in the 2nd week (section 8.8.5)
6.4.2 Some specific problems with *P. aeruginosa*

6.4.2i Which antibiotic combination should be chosen?

A number of morphotypes of *P. aeruginosa* may be present in sputum: antibiotic sensitivity patterns may differ between morphotypes and colonies of the same morphotype may have different sensitivity patterns.\(^{20}\) [3] The pragmatic solution is to choose a combination of two antibiotics to which the majority of morphotypes cultured from the sputum are sensitive. There is a concern that the use of a single antibiotic may be associated with increased levels of antibiotic resistance in *P. aeruginosa*.\(^{21}\) [2+] A systematic review of single vs. combination antibiotics found no difference in efficacy or safety but a trend towards increased antibiotic resistance following single agent use.\(^{22}\) [1++] It seems sensible to choose two antibiotics with differing mechanisms of action, such as a beta-lactam and an aminoglycoside. Where the organisms are sensitive to beta-lactams, there is some evidence that meropenem is more effective than ceftazidime, with a greater improvement in FEV1 and more rapid onset of improvement.\(^{23}\) [1+]

6.4.2ii Multiple antibiotic resistance

This is defined as resistance to all agents in 2 of the major classes of anti-pseudomonal antibiotics namely: beta-lactams (including imipenem, meropenem and aztreonam); the aminoglycosides (specifically tobramycin); and/or the quinolones (generally ciprofloxacin).\(^{16}\) [4] *P. aeruginosa* may show resistance to a single antibiotic *in vitro* but a combination of two or more antibiotics may kill the organism. Resistance to a number of antibiotic combinations may be assessed *in vitro*, using multiple combination bactericidal testing (MCBT). A randomised controlled trial comparing treatment of the patient’s “resident” strain of *P. aeruginosa* according to MCBT of the last clinic specimen vs. physician preference did not show an improved outcome with MCBT.\(^{24}\) However, when analysis was restricted to those patients who received a bactericidal antibiotic according to the sensitivity patterns of organisms isolated during the current exacerbation (rather than those found at the last clinic visit) there was an improved outcome in the MCBT group. This subgroup analysis should be interpreted with caution. [1++]

6.4.2iii Sputum sensitivities may be discordant with the outcome of antibiotic treatment in the patient

It is a frequent clinical observation that patients with CF may improve clinically, even when the *P. aeruginosa* present in their sputum is not fully sensitive to the antibiotics they have received. It has been shown that there is no relationship between the susceptibility of *P. aeruginosa* to ceftazidime and tobramycin, on a sample taken prior to an exacerbation and improvement in FEV1.\(^{10}\) [2+] The patient may prefer an antibiotic combination which they have received previously, with good symptomatic improvement.

6.5 What dose, for how long, and in what setting should antibiotics be given?

CF patients often need higher doses on antibiotics than other patients, for a number of reasons. Firstly, they have an increased volume of distribution, such that higher doses are needed to achieve the same serum levels. Secondly, they eliminate antibiotics more rapidly (particularly aminoglycosides), and so higher doses are required to maintain therapeutic serum levels. Thirdly, unlike “simple” infections in other patients, many CF patients have “chronic” infection with pathogens that may require higher doses of antibiotics for a prolonged period. Intravenous antibiotics are usually administered for 10–14 days in patients with CF. There are no randomised controlled trials of treatment duration, though much of the improvement in lung function is seen within the first 7 days.\(^{23}\) However, shorter courses may lead to the next course of intravenous antibiotics being needed
much sooner. A minimum of 10–14 days of intravenous antibiotics is recommended and older or sicker patients may need 3 or more weeks of treatment. When intravenous antibiotics are administered at home there is less disruption to patient and family and this option is cheaper.\textsuperscript{25} A Cochrane review found no difference in outcome between home and hospital treatment, however this should be interpreted with caution as there were few trials.\textsuperscript{26} Some patients may be too ill to receive home antibiotics. Before home treatment is agreed the patient or a key family member must be trained to administer the antibiotics and support from a specialist nurse or equivalent should be available. Antibiotics ready prepared in an infusion device are preferable.

Acute anaphylactic reactions to antibiotics in CF are uncommon, and do not usually occur with the first dose. Patients offered repeat home IV treatment with the same antibiotics may not need to have the first dose of each in hospital. In some cases the entire course of intravenous treatment (including the first dose) may be given at home, but this practice may not be used in all centres and may not be appropriate for all patients. However, where the entire course of intravenous treatment is given at home, the CF team must ensure that the patient and family have been trained in the management of anaphylaxis and an adrenaline “pen” should be dispensed (and regularly checked to make sure the expire date has not passed).\textsuperscript{27} Some centres give anaphylaxis training and an adrenaline pen to all patients on home intravenous antibiotics but costs and logistics may preclude many centres from doing this. It is advisable to give the first dose of a new antibiotic under supervision in hospital, to allow unanticipated adverse reactions to be managed promptly.

6.6 How can we minimise the cumulative side effects of treatment?

With constantly improving survival in CF, complications due to repeated therapy are being increasingly reported. In particular, those due to the cumulative effects of aminoglycosides, which are nephrotoxic and ototoxic, are now coming to light. A national survey has shown that the incidence risk of acute renal failure in CF is between 4.6 and 10.5 cases/10,000 CF patients/year: this is considerably greater than the background rate in the general population (approximately one hundred times greater in children).\textsuperscript{28} The risk of renal failure in CF patients is significantly associated with the use of gentamicin (but not tobramycin) in the previous year.\textsuperscript{29} Between 31 and 42% of adult patients with CF – who have no symptoms of renal problems – have impaired renal function.\textsuperscript{30} Renal impairment is related to previous aminoglycoside use and this appears to be potentiated by the coadministration of intravenous colistin.\textsuperscript{30} Renal tubular damage, related to aminoglycoside use may lead to symptomatic hypomagnesaemia in CF.\textsuperscript{31} A recent study also showed evidence of persistent renal tubular damage in CF patients who have CF related diabetes and those who had received repeated courses of intravenous colistin.\textsuperscript{32} Significant hearing impairment is found in 17% of CF patients (children and adults). Hearing impaired patients have received significantly more courses of aminoglycoside treatment (20 courses vs. 9 in the group with normal hearing).\textsuperscript{33} The use of an aminoglycoside may also be associated with vestibular toxicity.\textsuperscript{34} Drug allergy is commonly seen with beta-lactam antibiotics, particularly piperacillin and piperacillin/tazobactam combinations.\textsuperscript{35} Whilst \textit{P. aeruginosa} employs a number of strategies to achieve antibiotic resistance, including biofilm formation, transmissible resistant strains and inducible genes for antibiotic resistance, there is no doubt that cumulative lifetime exposure to antibiotics has an important role through selective pressure for resistance.

How may these cumulative effects be reduced or prevented? There is evidence from a randomised controlled trial of once vs. three times daily tobramycin (the TOPIC study) that once daily treatment is equally efficacious and is associated with less acute nephrotoxicity in children,\textsuperscript{36} but the study showed no difference in ototoxicity between the two regimens.\textsuperscript{37} Prior exposure to gentamicin but not tobramycin increases the risk of renal failure\textsuperscript{38} and around half of isolates of \textit{Paeruginosa} from UK CF patients are resistant to gentamicin.\textsuperscript{39} Hence, tobramycin and not gentamicin should be the
aminoglycoside of choice for intravenous treatment in CF. Co-administration of nephrotoxic drugs (such as an aminoglycoside and ibuprofen) should be avoided where possible. Measurement or estimation of glomerular filtration rate (GFR) should be done annually along with plasma magnesium as a measure of renal tubular function. Care should be taken to use an appropriate formula and it should be recognised that formulae may underestimate renal impairment. Ototoxicity is likely to be related to the accumulation of the aminoglycoside in the cochlear hair cells of the inner ear, where its half life is measured in months. It may be reasonable therefore to restrict the use of an aminoglycoside to alternate courses of intravenous antibiotics, where the patient’s clinical condition permits. An annual pure tone audiogram should be considered for patients receiving frequent courses of an intravenous aminoglycoside. Drug allergy cannot be prevented but can be managed with an appropriate desensitisation regimen.

6.7 Recommendations

- CF patients suffering from a pulmonary exacerbation or from persisting low grade symptoms, unresponsive to oral antibiotics should receive intravenous antibiotics. Intravenous treatment should accommodate (where possible) the commitments of the patients and family such as work, exams and holidays [D].

- Patients who experience frequent exacerbations may benefit from regular rather than as required intravenous antibiotics but regular treatment is not indicated for most patients [D].

- For organisms other than *P. aeruginosa* a single agent may be appropriate. For *P. aeruginosa*, a combination of 2 antibiotics with a different mechanism of action should be used for intravenous treatment in CF patients. Ceftazidime and tobramycin are commonly used but meropenem and colistin is a suitable alternative combination [A].

- Home treatment is an acceptable (and cheaper) option for selected patients. First doses of repeated antibiotic courses do not need to be given in hospital [D].

- A once daily aminoglycoside regimen may be more convenient for most patients, though some find the use of a 30 minute infusion difficult. Once daily tobramycin is associated with less acute nephrotoxicity in children. Tobramycin is the aminoglycoside of choice and gentamicin should be avoided. Co-administration of other nephrotoxic drugs should be avoided [A].

- Plasma creatinine should be measured before the 1st dose of tobramycin and again before the 8th dose. Trough and peak serum aminoglycoside levels should be measured depending upon the dosing regimen used [B] (section 6.4.1).

- In patients receiving repeated courses of nephrotoxic antibiotics, glomerular filtration rate should be measured or estimated annually, along with plasma magnesium as a measure of renal tubular function [B].

- Consideration should be given to an annual pure tone audiogram in patients receiving frequent courses of an aminoglycoside [B].

- In order to reduce cochlear and vestibular toxicity the use of an aminoglycoside should be restricted to alternate courses of intravenous antibiotics, where the patient’s clinical condition permits [D].

- Drug allergy should be managed with an appropriate desensitisation regimen [D].
6.8 References


7. OTHER INFECTIONS

7.1 Management of respiratory exacerbations in patients with *Burkholderia cepacia* complex

7.1.1 Introduction

Management of *Burkholderia cepacia* infection requires awareness of problems that may arise in culture and identification, including the consequences of recent taxonomic advances. Briefly, isolates presently identified as ‘*B. cepacia*’ by conventional methods comprise several closely related bacterial species (sometimes referred to as genomovars) (Table 7.1). Because of their phenotypic similarity they are collectively referred to as the *B. cepacia* complex (Bcc).

**Table 7.1: Taxonomy of the Burkholderia cepacia complex – genomovar status and species name.**

<table>
<thead>
<tr>
<th>Genomovar</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td><em>Burkholderia cepacia</em></td>
</tr>
<tr>
<td>II</td>
<td><em>Burkholderia multivorans</em></td>
</tr>
<tr>
<td>III</td>
<td><em>Burkholderia cenocepacia</em></td>
</tr>
<tr>
<td>IV</td>
<td><em>Burkholderia stabilis</em></td>
</tr>
<tr>
<td>V</td>
<td><em>Burkholderia vietnamiensis</em></td>
</tr>
<tr>
<td>VI</td>
<td><em>Burkholderia dolosa</em></td>
</tr>
<tr>
<td>VII</td>
<td><em>Burkholderia ambifaria</em></td>
</tr>
<tr>
<td>VIII</td>
<td><em>Burkholderia anthina</em></td>
</tr>
<tr>
<td>IX</td>
<td><em>Burkholderia pyrocinia</em></td>
</tr>
<tr>
<td>X</td>
<td><em>Burkholderia ubonensis</em></td>
</tr>
<tr>
<td>?</td>
<td><em>Burkholderia lateens</em></td>
</tr>
<tr>
<td></td>
<td><em>Burkholderia diffusa</em></td>
</tr>
<tr>
<td></td>
<td><em>Burkholderia arboris</em></td>
</tr>
<tr>
<td></td>
<td><em>Burkholderia seminalis</em></td>
</tr>
<tr>
<td></td>
<td><em>Burkholderia metallica</em></td>
</tr>
</tbody>
</table>

The outcome of Bcc infection in patients with CF is variable. Some individuals experience frequent exacerbations of their pulmonary disease, similar to those seen in patients with chronic *P. aeruginosa* infection; others have no symptoms or succumb to the rapidly fatal pneumonia known as ‘cepacia syndrome’. Some members of the Bcc are more closely associated with ‘cepacia syndrome’ and patient-to-patient spread, in particular *Burkholderia cenocepacia*. Other species such as *Burkholderia multivorans* have also been associated with ‘cepacia syndrome’ and some, such as *Burkholderia dolosa* appear as invasive *in vitro* as *B. cenocepacia*. Chronic infection with *B. dolosa* has also been associated with accelerated decline in lung function in patients with CF.

Studies suggest that the epidemiology of Bcc has changed in recent years in CF units. Successful segregation policies have resulted in a decline in the prevalence of *B. cenocepacia* and in many European CF centres the most common Bcc species is now *B. multivorans*. Even in countries where *B. cenocepacia* remains the predominant species, such as the USA, most recent acquisitions have been with *B. multivorans*. Genotyping evidence also suggests that most isolates of *B. multivorans* appear largely unrelated between different patients, suggesting possible acquisition from the environment rather than from other patients with CF. Isolates of Bcc can be found in a variety of environmental niches such as soil and water, but exactly how patients with CF acquire many members of the Bcc such as *B. multivorans* remains uncertain.
Unfortunately most organisms within the *B.cepacia* complex exhibit high levels of resistance to antipseudomonal antibiotics, including inherent resistance to colistin.\textsuperscript{21–23} Some UK centres have reported pan-resistance in >80% of patient isolates.\textsuperscript{24} In general environmental strains are more susceptible than clinical strains.\textsuperscript{25;26} Resistance can be observed in all genomovars,\textsuperscript{27} although some studies have suggested that resistance may be highest with *B.dolosa*.\textsuperscript{26} The most consistently active agents *in vitro* appear to be ceftazidime, piperacillin-tazobactam, meropenem, imipenem, ciprofloxacin, trimethoprim, cotrimoxazole, and tetracyclines.\textsuperscript{23;26;28–32} Levels of resistance to aminoglycosides are high. There are also anecdotal reports of the use of temocillin for treating Bcc exacerbations, although the clinical improvements observed were relatively modest.\textsuperscript{33}[3]

Some combinations of two or three antibiotics have shown synergy against Bcc.\textsuperscript{34} In this study meropenem in particular was shown to be bactericidal in combination with ceftazidime, amikacin or minocycline against >70% of isolates. Combinations of tobramycin plus meropenem plus a third agent were synergistic against >80% of isolates. However, other studies, using different laboratory methods, have failed to demonstrate such levels of synergy.\textsuperscript{32} In this later study of 2,621 Bcc isolates from 1,257 persons with CF, synergy was observed against less than 20% of isolates for two-drug combinations. The clinical significance of synergy is also questionable. A randomised, double-blind, controlled trial of selection of treatment for exacerbations caused by multi-resistant bacteria (including Bcc) failed to show a benefit for those regimens selected on the basis of synergy testing versus those chosen on the basis of routine susceptibility tests.\textsuperscript{35}[1+] 

There are anecdotal reports that some isolates of Bcc, particularly *B.multivorans*, can be successfully eradicated with early aggressive antibiotic therapy before chronic infection becomes established.\textsuperscript{36} Patients were treated with a regimen of three intravenous antibiotics (e.g. tobramycin plus meropenem plus ceftazidime) for two weeks. There is also anecdotal evidence that eradication can be enhanced by giving aerosolized amiloride and tobramycin in combination.\textsuperscript{37}[3]

Little data exist on optimum therapeutic approaches to the management of ‘cepacia syndrome’. Interestingly one study of Bcc bacteraemia suggested persons with CF were less likely to die within 14 days of bacteraemia than those with other co-morbid factors.\textsuperscript{38} The same study also suggested that treatment with cotrimoxazole was associated with reduced mortality. [2-] There are also anecdotal reports that administration of corticosteroids in conjunction with antibiotic therapy may improve survival\textsuperscript{39} and combined intravenous and nebulised antibiotics have been used.\textsuperscript{40}[3]

### 7.1.2 Recommendations for the treatment of *Burkholderia cepacia* complex

- **Antimicrobial therapy should be directed by *in vitro* sensitivities where available [C].**
- **Combination therapy should be used for treatment of Bcc exacerbations and ‘cepacia syndrome’ [C].**
- **The routine use of synergy testing to guide therapy of Bcc cannot be recommended at this time [A].**
- **The use of eradication therapy for all new growths of Bcc should be considered [D].**
7.2 Respiratory infection with meticillin-resistant *Staphylococcus aureus*

### 7.2.1 Introduction

This section deals with the antibiotic treatment of infection with meticillin-resistant *Staphylococcus aureus* (MRSA) in CF patients. For details of prevalence, risk factors, screening eradication and infection control, please see the recent (April 2008) UK Cystic Fibrosis Trust Infection Control Working Group publication “Meticillin-resistant *Staphylococcus aureus* (MRSA).”

The last ten years has seen a major increase in MRSA infections in the non-CF population in the UK. As a result there are strict national guidelines for the control of MRSA infection in hospitals which appear successful in contributing to control of infection in a CF centre. The prevalence of CF related MRSA infection appears to be rising with values quoted between 3 to 10% with a recent Belgian epidemiology study suggesting an overall prevalence of 5%.

Whilst there is no evidence that MRSA infection increases mortality in people with CF, there is debate about the possibility of increased morbidity. One large study in adults found no correlation with clinical deterioration, but a paediatric cohort infected with MRSA have been shown to have significantly higher intravenous antibiotic requirements and impaired growth compared to non-infected controls.

Even in the absence of clinical deterioration, MRSA infection results in significant difficulties in antibiotic choice and delivery of care. MRSA infection is not a complete contraindication for transplantation, but remains a relative contraindication in some units.

It is important to aim to reduce the risk of MRSA colonisation and to avoid chronic infection in people with CF in order to ensure suitability for transplantation, to limit systemic exposure to vancomycin (in the context of requirements for aminoglycoside use and potential renal toxicity) and to limit the development of a source of spread to other people at risk of severe infection in the hospital.

Hospitals should follow national guidelines for the control of MRSA. Special efforts should be made to prevent the spread of MRSA among patients with cystic fibrosis. This may require special isolation facilities in Specialist CF Centres and CF Clinics and regular screening of patients for carriage of the organism.

### 7.2.2 Treatment

(See UK CF Trust Infection Control Working Group MRSA document section 6) Meticillin-resistant *Staphylococcus aureus* are resistant to all beta-lactam antibiotics and often to other agents including aminoglycosides and macrolides. The Joint Working Party of the British Society for Antimicrobial Chemotherapy, Hospital Infection Society and Infection Control Nurses Association have produced guidelines for treatment of MRSA in the UK. The recommendation from that group is that agents such as tetracyclines (e.g. doxycycline) and clindamycin are used in MRSA respiratory tract infections, in bronchiectasis without pneumonia. Glycopeptides (e.g. vancomycin, teicoplanin) and linezolid were indicated for more severe respiratory tract infections (e.g., pneumonia). The choice of antibiotic could be guided by *in vitro* sensitivities.

Treatment of nasal carriage is best achieved with nasal mupirocin although resistance can arise. A variety of eradication protocols in CF have been suggested. Solis *et al.* reported a 55% eradication rate employing nebulised vancomycin whilst Macfarlane *et al.* reported the success of a
A three-step protocol using oral rifampicin and fusidic acid for 5 days, followed by a repeat course if unsuccessful, with a final step of intravenous teicoplanin, if oral treatment failed. This regimen was associated with a 94% success rate. None of these regimens have been submitted to randomised control trials and each unit may require modifications of the regime depending on local susceptibility data and practice. Chronic carriage can be reduced by prolonged therapy with oral rifampicin and fusidic acid.54

7.2.3 Recommendations – eradication and treatment of MRSA

- **Surveillance.** *(See UK CF Trust Infection Control Working Group MRSA document41 section 5).* Regular monitoring of respiratory specimens from all patients with CF for MRSA. Nasal, throat and skin swabs performed as per local infection control guidelines. [C] Follow hospital isolation policies [D].

- **Eradication.** At first isolate, or in a person who has been free of MRSA following previous treatment, aim to eradicate the organism. The regimen should include standard topical treatment and either combination oral therapy with rifampicin and fusidic acid or nebulised vancomycin or a combination of all three. *(section 8.3)* [C] In CF patients aged over 12 years, a tetracycline may be used if the organism is susceptible [C].

- **Treatment of chronic MRSA infection.** For acute exacerbations, include intravenous teicoplanin or vancomycin [C]. *(Drug monitoring can be performed for teicoplanin to ensure appropriate levels).* People with persistent MRSA colonisation may benefit from prolonged therapy with combination oral rifampicin and fusidic acid and can be rendered MRSA-free [C]. Long term single agent use of trimethoprim, rifampicin or fusidic acid MUST be avoided.

7.2.4 Recommendations – regimens for treating MRSA colonisation/infection of non-respiratory sites

*(See UK CF Trust Infection Control Working Group MRSA document41 section 6.1).*

- **Nasal Carriage:** 2% nasal mupirocin – each nostril 3 times daily for 5 days
  
  If two treatment failures (or isolate is mupirocin-resistant): naseptin cream (0.5% neomycin plus 0.1% chlorhexidine)
  
  Treat all nasal carriers for skin carriage

- **Skin Carriage:** Bathe for five days with an antiseptic detergent.
  
  Options include:
  
  - 4% chlorhexidine
  - 2% triclosan
  - 7.5% povidone-iodine
  
  Wash hair twice weekly with one of the above
  
  Apply hexachlorophene powder (e.g. 0.33% SterZac) to axillae/groins
## Table 7.2 Published data on eradication strategies used against MRSA in patients with Cystic Fibrosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maiz et al.55</td>
<td>Aerosolised vancomycin 250 mg in 4 ml sterile water nebulised twice daily* for 10 minutes</td>
<td>17 months</td>
<td>Successful eradication in 7 of 12 patients for mean of 12 months</td>
</tr>
<tr>
<td>Solis et al.52</td>
<td>Aerosolised vancomycin 4 mg/kg/dose diluted in 0.9% sodium chloride 4 times daily*</td>
<td>5 days</td>
<td>Successful eradication in 7 of 12 patients for mean of 12 months</td>
</tr>
<tr>
<td></td>
<td>*Preceded by nebulised terbutaline 500 μg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tracheostomy: 2% vancomycin cream twice daily; change tube</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nasal carriage: 2% mupirocin cream 4 times daily OR 2% vancomycin cream 4 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal carriage: 2% vancomycin paste OR 2% vancomycin gel OR 5 mg vancomycin lozenges 4 times daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal carriage: 40 mg/kg/day vancomycin oral suspension in 4 divided doses</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin carriage: 4% chlorhexidine bath alternate days (dilute 1/100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garske et al.54</td>
<td>Rifampicin 600 mg once daily orally plus sodium fusidate 250–500 mg twice daily orally</td>
<td>6 months</td>
<td>Successful eradication in 5 of 7 patients for mean of six months</td>
</tr>
<tr>
<td>Macfarlane et al.53</td>
<td>Step 1: Topical therapy plus Fusidic Acid 50 mg/kg/day Rifampicin 20–40 mg/kg/day</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 2: Repeat</td>
<td>5 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Step 3: IV Teicoplanin (section 8.3)</td>
<td>10–14 days</td>
<td></td>
</tr>
</tbody>
</table>

### 7.3. Respiratory infection with *Stenotrophomonas maltophilia*

#### 7.3.1 Introduction

Isolation of *S. maltophilia* from sputa of patients with CF has increased markedly since the early 1980s56 [2-] and some Specialist CF Centres now report a prevalence of over 20%.57;58 [3] The precise reasons for these increases are unclear but there is an association between the emergence of *S. maltophilia* in patients with CF and exposure to anti-pseudomonal antibiotics.59–62 [3] There is some evidence that the organism is acquired from a variety of environmental sources found both within the hospital and the community, particularly moist sites, such as taps, showerheads, plugholes and water itself.63 [3] Equipment used to deliver aerosolised antibiotics may also be a potential source of *S. maltophilia*.64;65 [3] There is no evidence of patient-to-patient transmission66–68 [3] and strict isolation protocols, such as those applied to patients colonised with *B. cepacia* and highly transmissible *P. aeruginosa*, are not necessary.

The clinical significance of *S. maltophilia* colonisation in CF remains an area of uncertainty. There have been no reports of acute deterioration in people with CF following acquisition of *S. maltophilia*. One retrospective review suggests that patients chronically colonised with *S. maltophilia* experience long-term deterioration in lung function, similar to that in *P. aeruginosa*-colonised patients69 [3] although the majority of studies have not shown this relationship.70–73 [3] There are anecdotal reports that gradual deterioration only occurs in those patients colonised with >10^6 cfu of *S. maltophilia* per ml of sputum.74 [3] However two large cohort studies using data from the Cystic Fibrosis Foundation Registry have found that, although those positive for *S. maltophilia* had more advanced disease, acquisition of the organism had no significant impact on short term (three years) survival75 nor did...
this result in an accelerated decline in respiratory function. 76

Unfortunately *S. maltophilia* is resistant to most anti-pseudomonal antibiotics. 77 In most studies only co-trimoxazole appears to have consistent activity, with >90% of isolates appearing susceptible *in vitro*, although a recent study specifically using isolates from persons with CF found high levels of resistance to cotrimoxazole. 78 [3] Minocycline, ticarcillin-clavulanate or aztreonam plus co-amoxiclav may also be active. The novel glycyycline antibiotic tigecycline has also been shown to have good *in vitro* activity against *S. maltophilia*. 79 [3] Combination therapy with ceftazidime plus an aminoglycoside or ciprofloxacina80 [4] and cotrimoxazole with ticarcillin-clavulanate or piperacillin-tazobactam81 [3] has been shown to be synergistic *in vitro* against some strains of *S. maltophilia*. Other recent *in vitro* studies have also suggested that azithromycin may be synergistic in combination with cotrimoxazole against 20% of *S. maltophilia* strains isolated from people with cystic fibrosis. 82 [3] However, susceptibility tests for *S. maltophilia* can give unreliable results depending on the method used and, as yet, it is not clear if *in vitro* susceptibility test results are a reliable predictor of clinical response. 83 [3]

**7.3.2 Recommendations (section 8.15)**

- **Given the continuing doubts about clinical significance of this organism and the potential toxicity of some of the agents, it would seem prudent to suggest that only those patients chronically infected with *S. maltophilia*, and who exhibit evidence of clinical deterioration in the absence of other causes, should receive antibiotic treatment specifically targeted at this organism [D].**

- **Unless contra-indicated by resistance or intolerance, co-trimoxazole is the usual drug of choice should treatment be indicated. [D] Alternatives include tetracyclines e.g. minocycline (not for children under 12 years), ticarcillin-clavulanate; and tigecycline [D].**

**7.4 Respiratory infection with *Achromobacter (Alcaligenes) xylosoxidans***

**7.4.1 Introduction**

The reported prevalence for *A. xylosoxidans* in CF centres is lower than for *S. maltophilia*, with rates usually less than 10%84–87 [3] although this appears to be rising. 88 [3] Little is known regarding routes of acquisition, although there are reports of cross-infection between patients. 89 [3] Uncertainty still remains regarding its clinical significance. Tan *et al* investigated the impact of chronic *A. xylosoxidans* infection in 13 patients in Leeds and found no evidence of attributable clinical deterioration two years post-acquisition. 90 [3] De Baets *et al* evaluated eight patients with chronic *A. xylosoxidans* infection and, although they required more courses of antibiotics, they could find no evidence of accelerated decline in respiratory function. 91 However, Ronne Hansen *et al* did find that *A. xylosoxidans* was associated with declining respiratory function if there was a rapid rise in specific precipitating antibodies in serum. 92 [3] *A. xylosoxidans* is often multi-resistant and clinical data is lacking regarding optimum therapy. *In vitro* data suggests that the most active agents may be minocycline; meropenem or imipenem; piperacillin-tazobactam; and chloramphenicol. 93 [3]
7.4.2 Recommendations

- Given the continuing doubts about clinical significance and the potential toxicity of some of the agents, it would seem prudent to suggest that only those patients chronically infected with A. xylosoxidans, and who exhibit evidence of clinical deterioration in the absence of other causes, should receive antibiotic treatment specifically targeted at this organism [D].

- Therapy should be targeted on the basis of susceptibility testing results [D].

7.5 Respiratory infection with Pandoraea sp.

7.5.1 Introduction

Pandoraea sp. are gram-negative bacilli that are increasingly isolated from CF sputa. They are inherently resistant to colistin and as such, can be isolated from selective media for B. cepacia complex, for which they can be mistaken.94 [3] An outbreak of Pandoraea apista involving six patients, four of whom clinically deteriorated, has been reported from the Danish CF Centre.95 [3] A single case of Papista bacteremia in a 16 year old male with CF has been reported.96 [3] There is also evidence that Papista can chronically colonize persons with CF for several years.97 [3] Little is known regarding the susceptibility and treatment of Pandoraea sp., although anecdotally they appear multi-resistant.98–99 [3]

7.5.2 Recommendations

- Pandoraea apista has been associated with clinically significant infection in CF. Therapy should be targeted on the basis of susceptibility testing results [D].

7.6 Influenza A infection

7.6.1 Introduction

Influenza A has a more significant impact on persons with CF compared to other individuals.100 However, there is little objective data regarding the use of antiviral agents in persons with CF. An analysis of studies assessing the efficacy of antiviral drugs targeted against influenza A (e.g. oseltamivir, zanamivir) have failed to show a significant benefit for 'high risk' children (in trials this was mostly those with asthma) in terms of reduction of duration of symptoms or number of secondary cases in contacts.101 [1+] Similarly, evidence for benefit in 'high risk' adults was inconclusive.102 [1+] In spite of these findings the use of antiviral drugs against influenza A is recommended in current National Institute for Clinical Excellence (NICE) guidelines for treatment of influenza-like illness (ILI) in those with chronic respiratory diseases.103 Further studies are needed to fully elucidate the role of these agents in children and adults with CF. There is no current evidence of benefit for the influenza vaccine in persons with CF.104 [1+] However, its use in those over six months of age is recommended by the European Cystic Fibrosis Society (ECFS) Vaccine Group.105 [4]
7.6.2 Recommendations

- **All persons with CF over six months of age should be vaccinated against influenza [D].**
- **All persons with CF presenting with an influenza like illness, when influenza is known to be circulating in the community, should be treated with an effective antiviral agent, provided they present within 48 hours of onset of symptoms [C].** Influenza prevalence data are available on the weekly influenza reports, which are circulated by the Health Protection Agency. Treatment is as follows: age 1–12 years – oseltamivir; age >12 years – oseltamivir or zanamivir.

7.7 Totally implantable intravenous access device (TIVAD) infections

7.7.1 Introduction

Totally implantable intravenous access device (TIVAD) infection is increasingly seen in CF units. Feedback from 30 of 42 adults with CF in whom TIVADs had been placed in Edinburgh revealed that two had devices removed because of infection. No details regarding the causative organisms were given. An Australian study reported 18 infectious complications in 57 TIVADs implanted in 44 children with CF. Five of these cases resulted in systemic infections (one each caused by *S.maltophilia*, *Flavobacterium* sp., *Candida parapsilosis*, *S.aureus*, and *P.aeruginosa*). All were successfully treated with line removal and appropriate antimicrobial therapy. Five systemic infections were also reported in a study of 65 PAS Ports inserted in 57 adults with CF over a five-year period in Leeds. The reported causes were *Candida* sp., (2 cases), *S.aureus* (1), *Paeruginosa* (1), and 1 unknown. All were treated with line removal and appropriate antimicrobial therapy. Two cases of *S.maltophilia* line infection were also reported from the Leeds CF Unit. Kariyawasam et al reported 16 (14%) infections of 115 TIVADs implanted into 74 adults with CF over a 13 year period at the Royal Brompton. Three were caused by *Candida* sp., 1 by *Paeruginosa* and the other 12 were clinically diagnosed without confirmatory microbiology. Devices were removed in conjunction with initiation of appropriate antimicrobial therapy.

The elevated risk of candidaemia in association with TIVADs in persons with CF has been highlighted in a number of historical reports. This risk is enhanced by other factors commonly associated with CF, such as diabetes mellitus, malnutrition, and broad-spectrum antibiotic therapy. The importance of removing TIVADs to effect cure of *Candida* sp. infections has been emphasised in treatment guidelines.

7.7.2 Recommendations

- **Infection of totally implantable intravenous access devices (TIVADs) complicated by bacteraemia/fungaemia should be treated, where possible, with early line removal and appropriate antimicrobial therapy, guided by culture and sensitivity results. Removal should be mandatory in cases of fungal infection [D].**

7.8 Non-tuberculous mycobacteria

7.8.1 Prevalence of non-tuberculous mycobacteria

Patients with chronic suppurative lung disease are potential subjects for non-tuberculous mycobacteria (NTM). Additional risk factors may be poor nutrition, increasing age and disease severity, frequent intravenous antibiotic treatments, diabetes mellitus and corticosteroid treatment,
although not all authors have found these factors to be relevant.\textsuperscript{116-121} [3] NTM are found in the respiratory secretions of up to 20\% of patients with CF, if appropriate isolation methods are used.\textsuperscript{122} [3] A multicentre North American study commenced in 1992 and completed in 1998 has confirmed the prevalence of NTM, defined as having at least one positive culture, in patients with CF as 13\% (128/986) which varied between CF clinics from 7\% to 24\%. A total of 2.5\% of patients (25/986) fulfilled the American Thoracic Society (ATS) criteria at that time of either 2 positive cultures and a positive smear or 3 positive cultures. \textit{Mycobacterium avium} was cultured most frequently (72\%) with \textit{Mycobacterium abscessus} being the next most common (16\%).\textsuperscript{123} [2+] In this largest study of prevalence of NTM in CF the patients with positive cultures were older and had relatively mild lung disease but worse nutritional status. In addition they were more likely to have concomitant \textit{S. aureus} infection rather than \textit{P. aeruginosa}.

\section*{7.8.2 Clinical significance of non-tuberculous isolates in sputa from patients with cystic fibrosis}

The significance of the isolation of non-tuberculous mycobacteria (NTM) from respiratory secretions remains unclear despite a number of clinical reports. Non-tuberculous mycobacteria are environmental organisms that have been recovered in soil, dust and drinking water systems. The recovery of NTM in sputum of a person with CF poses a diagnostic dilemma. The question arises as to whether the isolate represents transient contamination of the airways, colonisation, or true infection. There is no consistent evidence that antibiotic treatment is beneficial. The ATS criteria for diagnosis of disease have recently been revised.\textsuperscript{124} [4] Although not specifically designed for CF, they are helpful in guiding investigation. Minimum evaluation should include an HRCT scan, three or more sputum samples for acid fast bacilli analysis and exclusion of other disorders. In the case of individuals with CF and suspected NTM infection, it is important to first treat their usual pathogens and then assess whether anti mycobacterial therapy is warranted.

The largest study of NTM in the US revealed that FEV1 decline was no different overall in the short term in people with or without NTM infection but that all subjects with 3 or more positive cultures showed evidence of progression of disease on CT scan compared to controls.\textsuperscript{125} [2+] Thus a stepwise approach to consideration of therapy can be recommended (figure 7.1) with the first requirement being ATS microbiological criteria of at least two positive sputum cultures or a single positive lavage. The second step is the HRCT as an abnormal HRCT at baseline in keeping with NTM infection was predictive of progression in the American cohort.\textsuperscript{126} [2+]

Furthermore evidence that infection with \textit{Mycobacterium abscessus} is associated with significant disease allows further stratification for treatment.\textsuperscript{127-129} [3] We suggest the guide to assessment recommended by Olivier \textit{et al.}\textsuperscript{30} and suggest that this is validated in future studies. (figure 7.1)
7.8.3 Treatment (section 8.6)

NTM are almost always resistant in vitro to standard anti-tuberculous antibiotics. Treatment should be tailored to the specific species of NTM. The current ATS 2007 guidelines are extremely helpful in guiding therapy.132

*Mycobacterium avium complex* (MAC)

Initial therapy should be triple therapy with a macrolide (clarithromycin or azithromycin), rifampicin and ethambutol. (table 7.3)
Table 7.3 Drugs for treatment of *Mycobacterium avium* complex (MAC) (section 8.6)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paediatric dose (do not exceed adult dose)</th>
<th>Adult dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>7.5 mg/kg bd</td>
<td>1000 mg bd (same for child over 12y or 30 kg)</td>
<td>Oral</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>10 mg/kg od</td>
<td>500 mg od</td>
<td>Oral</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 mg/kg od</td>
<td>450 mg od if &lt;50kg 600 mg od if ≥50kg</td>
<td>Oral</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg/kg od</td>
<td>15 mg/kg od Maximum dose 1.5 g</td>
<td>Oral</td>
</tr>
</tbody>
</table>

An alternative three times weekly regimen can be used in less severe disease using clarithromycin 1000 mg (child 7.5 mg/kg bd) or azithromycin 500 mg (child 10 mg/kg od) along with ethambutol 30 mg/kg and rifampicin 600–900 mg (child 15 mg/kg) on Mondays, Wednesdays and Fridays. Ethambutol should not be used in children too young to report adverse effects on vision. Antibiotic susceptibility testing is not predictive of clinical response in MAC with the exception of macrolide susceptibility. Macrolide resistance confers less likelihood of clearing the organism. The major risk factor for macrolide resistance is macrolide monotherapy making it imperative that people with CF are adequately screened for NTM before azithromycin is used routinely for CF lung disease. The primary goal of therapy is 12 months of negative sputum cultures whilst on therapy. Sputum must be checked on a regular basis. In refractory severe disease parenteral therapy with amikacin or streptomycin can be considered. When there is drug intolerance moxifloxacin and linezolid have been used.

*Mycobacterium abscessus*

Infection with *Mycobacterium abscessus* is more likely to result in progressive lung disease. Episodes of fever and systemic upset, with rapid fulminant disease, can occur. Microbiological cure is unlikely and treatment is aimed at improving clinical wellbeing. Treatment for *M. abscessus* consists of an induction phase with IV amikacin, in combination with IV meropenem or IV cefoxitin and clarithromycin 500 mg bd for three to four weeks minimum.

Maintenance therapy with nebulised amikacin, oral clarithromycin and another agent to which the organism is sensitive is recommended. The usual dose of nebulised amikacin is 500 mg bd (250 mg bd in younger children). The injectable preparation (250 mg/ml) should be used and made up to 4 ml with 0.9% sodium chloride (sections 5.6 & 8.6). Intermittent courses of the IV agent will be required (table 7.4 & sections 8.6 & 8.8).

Table 7.4 Drug treatment of *M. abscessus*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Paediatric dose (do not exceed adult dose)</th>
<th>Adult dose</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>10 mg/kg (max 500 mg) tds</td>
<td>7.5 mg/kg (max 750 mg) bd</td>
<td>IV</td>
</tr>
<tr>
<td>Meropenem</td>
<td>40 mg/kg tds</td>
<td>2 g tds</td>
<td>IV</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>40 mg/kg qds</td>
<td>2–3 g qds (max 12 g per day)</td>
<td>IV</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>7.5 mg/kg bd</td>
<td>500 mg bd</td>
<td>IV</td>
</tr>
</tbody>
</table>

Other agents which have been used for *M. abscessus* include linezolid and tigecycline. Further research is required to find the optimum regimen.
7.8.4 Recommendations

- Screen all patients with CF, who can produce sputum, for non-tuberculous mycobacteria at their Annual Review [D].

- Check sputum for acid fast bacilli if there is unexplained deterioration and if there is no sputum consider bronchoscopy and lavage to exclude NTM infection. Where acid fast bacilli are found, ensure that infection with Mycobacterium tuberculosis is excluded by culture or PCR [D].

- The decision to treat is based on clinical grounds. Treat patients who are deteriorating clinically or on CT and unresponsive to treatment for conventional CF respiratory pathogens, and who have repeatedly positive cultures or smears for NTM [D].

- Continue the antibiotic treatment for 12 to 18 months once cultures negative whilst on treatment [D].

- Consider monitoring drug levels if sputum fails to become negative [D].

7.9 Aspergillus

Aspergillus is a ubiquitous fungus, found in soil, water, the air and rotting vegetation. The vast majority of clinical disease is associated with Aspergillus fumigatus, although other species, such as Aspergillus flavus, Aspergillus terreus, and Aspergillus niger, may occasionally be isolated from clinical samples. In persons with CF the most commonly encountered problem is allergic bronchopulmonary aspergillosis (ABPA). Other clinical presentations are also recognised, including invasive pulmonary aspergillosis, aspergillus bronchitis, and aspergilloma.

7.9.1 Prevalence and risk factors for allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is an immune-mediated bronchial disease causing bronchiectasis as a result of exposure to *A.fumigatus*. This is often associated with increased respiratory symptoms due to wheeze, mucus plugging and non specific infiltrates and this can have a detrimental effect on lung function. Prevalence in CF is reported to be between 2–8%. The successful treatment of *S.aureus* and early *P.aeruginosa* colonization seems to increase the likelihood of respiratory cultures becoming positive for *A.fumigatus*, although positive respiratory cultures for *A.fumigatus* are not an essential pre-requisite for the diagnosis of ABPA. Significant risk factors associated with ABPA include increasing age co-colonization with *S.maltophilia* [3] and non-tuberculous mycobacteria [3] but climatic and geographical factors, including humidity, have not been shown to be significant.

Early recognition and treatment prevents long-term complications. The onset of ABPA can be fulminant or insidious, with serological and X-ray features preceding clinical symptoms. Annual screening usefully identifies the progression of allergic sensitisation and tests should be considered when acute exacerbations are atypical or poorly responsive to appropriate antibacterial therapies.
7.9.2 Diagnosis of ABPA

The Cystic Fibrosis Foundation Consensus Conference in 2001 produced diagnostic criteria for ABPA. A ‘classic case’ was defined as follows:

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, decline in pulmonary function, increased sputum) not attributable to another aetiology.
- Serum total IgE concentration of >1000 IU/mL (2400 ng/mL), unless patient is receiving systemic corticosteroids (if so, retest when steroid treatment is discontinued).
- Immediate cutaneous reactivity to Aspergillus (prick skin test wheal of 13 mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or in vitro presence of serum IgE antibody to A. fumigatus.
- Precipitating antibodies to A. fumigatus or serum IgG antibody to A. fumigatus by an in vitro test.
- New or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

Minimum diagnostic criteria were also defined as:

- Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another aetiology.
- Total serum IgE concentration of >500 IU/mL (1200 ng/mL). If ABPA is suspected and the total IgE level is 200–500 IU/mL, repeat testing in 1–3 months is recommended. If patient is taking steroids, repeat when steroid treatment is discontinued.
- Immediate cutaneous reactivity to Aspergillus (prick skin test wheal of 13 mm in diameter with surrounding erythema, while the patient is not being treated with systemic antihistamines) or in vitro demonstration of IgE antibody to A. fumigatus.
- One of the following: (a) precipitins to A. fumigatus or in vitro demonstration of IgG antibody to A. fumigatus; or (b) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

The following suggestions for screening were also made:

- Maintain a high level of suspicion for ABPA in patients >6 years of age.
- Determine the total serum IgE concentration annually. If the total serum IgE concentration is >500 IU/mL, determine immediate cutaneous reactivity to A. fumigatus or use an in vitro test for IgE antibody to A. fumigatus. If results are positive, consider diagnosis on the basis of minimal criteria.
- If the total serum IgE concentration is 200–500 IU/mL, repeat the measurement if there is increased suspicion for ABPA, such as by a disease exacerbation, and perform further diagnostic tests (immediate skin test reactivity to A. fumigatus, in vitro test for IgE antibody to A. fumigatus, A. fumigatus precipitins, or serum IgG antibody to A. fumigatus, and chest radiography).
7.9.3 Treatment of ABPA

Treatment for ABPA in CF can be divided into two components; attenuation of the inflammatory and immunological processes with corticosteroids and attenuation of the antigen burden with the use of antifungal therapy.\textsuperscript{147} [4]

Individuals with ABPA often respond well to oral prednisolone,\textsuperscript{148–151} [3] but prolonged and repeated corticosteroid use increases the risk of diabetes mellitus, osteoporosis and impaired growth. The efficacy of inhaled corticosteroids remains uncertain.\textsuperscript{152} [4]

The risks of corticosteroids may be partly offset by using antifungal therapy. Studies suggest that antifungals such as itraconazole may be beneficial for those with CF and ABPA.\textsuperscript{151;153–155} [3] To date, none of the studies in persons with CF have been randomised and controlled.\textsuperscript{156} [1+] However, an analysis of randomised, controlled trials of itraconazole treatment of ABPA, in persons with asthma, has shown that it modifies the immunological reaction and reduces the need for corticosteroid therapy over a short-term period.\textsuperscript{157} [1+] There is evidence that oral itraconazole is poorly absorbed by persons with CF, particularly children.\textsuperscript{158} [2+] Therefore it is recommended that serum levels are measured during therapy.\textsuperscript{159} [4] Although the association between serum levels and clinical outcome in ABPA is not clearly defined,\textsuperscript{160} [3] a level above 250 ng/mL, after steady state plasma concentrations are achieved, is seen as desirable.\textsuperscript{158} [2+] More recent studies have suggested voriconazole may be used instead.\textsuperscript{161} [3] It has good oral bioavailability but, like itraconazole, has a significant number of interactions with other drugs.\textsuperscript{162} [4]

Nebulised antifungal agents such as amphotericin B have been used when response to conventional therapy is poor.\textsuperscript{163} [3] Further studies are needed to determine the optimum use of antifungal agents for treating ABPA in CF.

7.9.4 Recommendations for management of ABPA (section 8.14)

- **Corticosteroids should be used for all exacerbations of ABPA in CF unless there is a contraindication to their use [B].**

- **Initial corticosteroid therapy**: 0.5–1 mg/kg/day oral prednisolone equivalent up to a maximum of 60 mg for 1–2 weeks, then convert to 0.5–1 mg/kg/day prednisolone equivalent every other day for 1–2 weeks, then taper on the basis of IgE, chest radiography, spirometry, and pulmonary symptoms. An attempt should be made to begin to taper off corticosteroids in 2–3 months. Avoid enteric coated prednisolone [B].

- **If there is no response to initial corticosteroid therapy the following should be considered [C]:**
  - Alternative causes for the symptoms.
  - Increasing the dose of corticosteroids.
  - The use of enteric-coated prednisolone.\textsuperscript{164} [4]
  - The addition of antifungal therapy.

- **Antifungal therapy with itraconazole should be added to therapy if there is a slow or poor response to corticosteroids, for relapse of ABPA, in corticosteroid-dependent ABPA, and in cases of corticosteroid toxicity [C].**

- **The initial dose of itraconazole should be 5 mg/kg/day, which may be given once daily unless the dose exceeds 200 mg/day, in which case it should be given twice daily. The daily dose should not exceed 400 mg/day unless low serum itraconazole levels are obtained. The duration of therapy should be 3–6 months [C].**
• It is important to assess the clinical response after itraconazole withdrawal to assess whether it is still beneficial (e.g., prevents relapse and is corticosteroid-sparing) [C].

• For patients receiving itraconazole, liver function tests should be obtained before therapy and should be repeated whenever there is any suspicion of liver dysfunction. Routine liver function testing after 1 month and then every 3–6 months if therapy continues should be considered [C].

• Concomitant medications should be meticulously reviewed to avoid a drug-drug interaction and doses of concomitant medications and itraconazole should be adjusted accordingly. This may require determination of serum concentrations of concomitant drugs and/or itraconazole [C].

• Determination of itraconazole concentrations should also be considered when there is a lack of clinical response or if there is concern about adequate drug absorption or patient compliance. Blood should be drawn 4 hours after a dose; at steady state, achieved during the second week of therapy, random samples may be useful [C].

• For those whom antifungal therapy is indicated and there is evidence of poor absorption of itraconazole, oral voriconazole could be considered as an alternative. The oral dosage schedule is as follows:
  • Children <12 years of age: 200 mg bd
  • Patients ≥12 years and <40 kg: 200 mg bd for one day and then 100 mg bd;
  • Patients ≥12 years and >40 kg: 400 mg bd for 1 day and then 200 mg bd [C].

• There is insufficient evidence to support the routine use of aerosolized amphotericin B for treating ABPA in CF [C].

• General advice about reducing exposure to environmental sources of A. fumigatus spores (e.g., construction and renovation work, rotting vegetation, mucking out stables, other sources of dust) should be given [C].

7.9.5 Invasive pulmonary aspergillosis, aspergillomas, and aspergillus bronchitis

The spectrum of disease associated with Aspergillus sp. in CF is not limited to ABPA. Invasive pulmonary aspergillosis is a rare but serious form of aspergillosis mainly seen in immunosuppressed individuals. For persons with CF it is most likely to occur post transplantation, although this is relatively rare complication. Kanj et al reported one case in 21 persons undergoing lung transplantation in an American centre, and it accounted for only one of nine deaths in a case series of 55 persons with CF undergoing lung transplantation in an Italian centre. A more common presentation of Aspergillus sp. post-lung transplantation is an infection of the tracheal anastomosis, called tracheobronchial aspergillosis (TBA) and this has been reported in around 15% of persons with CF post-lung transplantation. There have also been anecdotal reports of invasive pulmonary aspergillosis occurring in apparently immunocompetent persons with CF. The occurrence of balls of Aspergillus mycelia, referred to as ‘aspergillomas’, which colonise damaged lung tissue, have also been reported in association with CF. More recently a novel presentation of ‘aspergillus bronchitis’ has been described in CF. Shoseyov et al reported six symptomatic individuals with positive respiratory cultures for A. fumigatus and radiological changes who did not fulfil diagnostic criteria for ABPA but responded to antifungal therapy.
7.9.6 Recommendations for invasive pulmonary aspergillosis, aspergillomas, and aspergillus bronchitis.

- The optimum therapy for non-ABPA presentations of *Aspergillus* sp. in persons with CF remains uncertain. The options for systemic antifungal therapy include amphotericin B (non-lipid or lipid preparations), voriconazole or caspofungin. In some presentations e.g., TBA, surgical debidement may also be of benefit [C].

7.9.7 Other fungi

Other fungi are an increasingly recognised complication of CF. *Scedosporium apiospermum* is frequently isolated from persons with CF and has been associated with a symptom complex similar to ABPA. Unlike *Aspergillus* sp. it has been difficult to isolate from the environment. Patients can become chronically colonised with the same strain which can persist in spite of antifungal therapy. It is also capable of causing invasive disease with high mortality post lung-transplant. Therapy is compromised by its resistance to many antifungal agents, including itraconazole and amphotericin B. Many isolates appear susceptible *in vitro* to voriconazole but this has been associated with clinical failure in patients and in animal models. Another fungus increasingly observed is *Exophiala dermatitidis*. However, its significance in CF remains uncertain.

7.9.8 Recommendations for unusual fungal infection

- If considered clinically significant, *Scedosporium apiospermum* should be treated with voriconazole or posaconazole [C].

7.10 References


March 2007


87. Ronne HC, Pressler T, Hoiby N, Gormsen M. Chronic infection with \textit{Achromobacter xylosoxidans} in cystic fibrosis patients; a retrospective case control study. \textit{J Cyst Fibros} 2006; \textbf{5}:245–51.

88. Ronne HC, Pressler T, Hoiby N, Gormsen M. Chronic infection with \textit{Achromobacter xylosoxidans} in cystic fibrosis patients; a retrospective case control study. \textit{J Cyst Fibros} 2006; \textbf{5}:245–51.


92. Ronne HC, Pressler T, Hoiby N, Gormsen M. Chronic infection with \textit{Achromobacter xylosoxidans} in cystic fibrosis patients; a retrospective case control study. \textit{J Cyst Fibros} 2006; \textbf{5}:245–51.


References:


8. PHARMACOPOEIA

Originally based on a document prepared by Amanda Bevan (Southampton). We are also grateful to Paula Hayes (Liverpool) and Helen Cunliffe (Leeds) for their advice. Also we thank Churchill Livingstone, publishers of Practical Guidelines for Cystic Fibrosis Care.1

If clinicians are unfamiliar with using a particular drug, it is important they read the summary of product characteristics (SPC) and discuss the drug’s use with the pharmacist involved with their Specialist CF Centre or CF Clinic and the hospital microbiology department. The SPC may be found in the electronic medicines compendium (http://emc.medicines.org.uk). Helpful guidance can also be found in the British National Formulary (http://www.bnf.org) and the British National Formulary for Children (http://bnfc.org)

8.1 Continuous anti-staphylococcal therapy

Flucloxacillin orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 3 year</td>
<td>125 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Recurrent growth of MSSA</td>
<td>50 mg/kg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

Preparations: 250 mg and 500 mg capsules, 125 mg/5 ml and 250 mg/5 ml suspensions (some children find Floxapen brand more palatable).

Administration: Take an hour before food or on an empty stomach.

Side-effects: Gastrointestinal upset and rarely sensitivity reactions. Hepatitis and cholestatic jaundice have been reported and may occur up to 2 months after stopping treatment.

Notes: Reduce dose or frequency in renal impairment – see specialist texts.

8.2 Treatment of asymptomatic Staphylococcus aureus isolates or minor exacerbations

Flucloxacillin orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 18 years</td>
<td>25 mg/kg (total daily dose may be given in 3 divided doses)</td>
<td>6 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>1–2 g</td>
<td>6 hourly</td>
</tr>
</tbody>
</table>

Additional Information: section 4.2.4
### Sodium Fusidate orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–1 year</td>
<td>15 mg/kg fusidic acid</td>
<td>8 hourly</td>
</tr>
<tr>
<td>1–5 years</td>
<td>250 mg fusidic acid</td>
<td>8 hourly</td>
</tr>
<tr>
<td>5–12 years</td>
<td>500 mg fusidic acid</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult</td>
<td>500 mg sodium fusidate or 750 mg fusidic acid (doubled for severe infections)</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

250 mg sodium fusidate tablets and 250 mg/5 ml fusidic acid suspension. As fusidic acid is incompletely absorbed doses are proportionately higher with suspension than tablets.

**Administration**

Take suspension with or after food.

**Side-effects**

Gastrointestinal upset, skin rashes, jaundice. Monitor liver function if prolonged therapy on high doses or hepatic impairment.

**Notes**

Traditionally used in combination with another antibiotic, e.g. flucloxacillin, to prevent resistance although scientific basis is doubtful. Avoid in liver disease.

### Rifampicin orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–1 year</td>
<td>5–10 mg/kg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>1–18 years</td>
<td>10 mg/kg (max 450 mg &lt;50 kg, max 600 mg ≥50 kg)</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>600 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

150 mg and 300 mg capsules, 100 mg/5 ml syrup.

**Administration**

Take half to one hour before food.

**Side-effects**

Flushing and itching, gastrointestinal reactions, hepatitis, thrombocytopenia, reddish discoloration of urine, sputum and tears (soft contact lens may be permanently stained).

**Notes**

Use in combination with another appropriate antibiotic (e.g. sodium fusidate) to prevent resistance. Rifampicin induces liver enzymes and therefore the elimination of other drugs (e.g. oral contraceptives) may be increased. Use with extreme caution in liver impairment, monitor liver function in prolonged treatment.

### Clindamycin orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>5–7 mg/kg (max 600 mg)</td>
<td>6 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>600 mg</td>
<td>6 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

75 mg and 150 mg capsules, 75 mg/5 ml suspension available from specialist importing companies.

**Administration**

Take capsules with plenty of water.

**Side-effects**

Nausea and vomiting, diarrhoea, pseudomembranous colitis (advise to discontinue and contact their doctor if diarrhoea occurs), blood dyscrasias, dermatitis and hypersensitivity reactions. Monitor liver and renal function if therapy is prolonged.

**Notes**

Dose reductions needed in renal or hepatic impairment.
8.3 Treatment of more severe exacerbations caused by *Staphylococcus aureus*

**Flucloxacillin intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>50 mg/kg</td>
<td>6 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>2–3 g</td>
<td>6 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 250 mg, 500 mg and 1 g vials.

**Administration** Take capsules with plenty of water.

**Side-effects** By slow intravenous injection over 3–4 minutes or infusion.

**Notes** See entry in section 8.1.

**Vancomycin intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>15 mg/kg (max 666 mg)</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>1 g</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 500 mg and 1 g vials.

**Administration** Must be given slowly over a minimum of 1 hour or at 10 mg/min for doses over 500 mg.

**Side-effects** Infusion related events: ‘red man’ syndrome if infusion given too quickly, nephrotoxicity, ototoxicity, reversible neutropenia and thrombocytopenia.

**Notes** Reduce dosage or avoid in renal impairment. Monitor level prior to 3rd dose – trough levels of 10–15 mg/l are acceptable although a trough up to 20 mg/l may be preferred in severe infections. (Always check local policy).

**Inhaled Vancomycin**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>4 mg/kg (max 250 mg)</td>
<td>6–12 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>250 mg</td>
<td>6–12 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 500 mg and 1 g vials.

**Administration** Dilute with sodium chloride 0.9% or sterile water.

**Side-effects** Bronchospasm.

**Notes** Precede dose with beta 2 agonist. Each reconstituted vial can be stored for 24 hours in the fridge.
**Teicoplanin intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>10 mg/kg (max 400 mg) for 3 doses then 10 mg/kg (max 400 mg)</td>
<td>12 hourly 24 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>400 mg for 3 doses then 400 mg</td>
<td>12 hourly 24 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 200 mg and 400 mg vials.

**Administration**
- Slow intravenous injection over 3–4 minutes.

**Side-effects**
- Gastrointestinal upset, Local reactions and hypersensitivity reactions.
- Monitor renal and auditory functions on prolonged treatment if renal impairment or other nephrotoxic or neurotoxic drugs given. See summary of product characteristics for full details. Some units monitor levels and alter does as appropriate if poor response to treatment.

**Notes**
- Caution if there has been hypersensitivity to vancomycin. Reduce dose in renal impairment – see specialist texts.

**Linezolid orally or intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–12 years</td>
<td>10 mg/kg (max 600 mg)</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult</td>
<td>600 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 600 mg tablet, 100 mg/5 ml suspension and 600 mg infusion.

**Administration**
- Infuse over 30–120 minutes.

**Side-effects**
- Gastrointestinal upset and headache. Haematopoietic disorders reported – full blood counts monitored weekly. Close monitoring needed if treatment for more than 10–14 days, pre-existing myelosuppression, severe renal impairment or receiving any drugs that may affect haemoglobin, blood counts or platelet function. Severe optic neuropathy may occur rarely particularly if treatment is continued for longer than 28 days. Linezolid is a reversible monoamine oxidase inhibitor.

**Notes**
- Oral gives similar levels to intravenous and is the preferred route of administration.

### 8.4 Treatment of asymptomatic *Haemophilus influenzae* carriage or mild exacerbations

**Amoxicillin orally** (only use when a SENSITIVE STRAIN of *H.influenzae* has been identified & there has been no recent history of infection with *S.aureus*)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–1 year</td>
<td>125 mg</td>
<td>8 hourly</td>
</tr>
<tr>
<td>1–7 years</td>
<td>250 mg</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Over 7 years &amp; adult</td>
<td>500 mg</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 250 mg and 500 mg capsules, 125 mg/5 ml, 250 mg/5 ml and 125 mg/1.25 ml suspensions.

**Side-effects**
- Nausea, diarrhoea and rashes.

**Notes**
- Reduce dose in renal impairment. Up to 20% of *H.influenzae* isolates are now resistant to amoxicillin – important to check sensitivity. Most have β-lactamase and will be susceptible to amoxicillin-clavulanic acid.
### Co-amoxiclav orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–1 year</td>
<td>0.5 ml/kg of 125/31 suspension</td>
<td>8 hourly</td>
</tr>
<tr>
<td>1–6 years</td>
<td>5 ml of 250/62 suspension</td>
<td>8 hourly</td>
</tr>
<tr>
<td>6–12 years</td>
<td>250/62 suspension 10 ml or (250/125) 1 tab plus amoxicillin 1x250 mg tab</td>
<td>8 hourly</td>
</tr>
<tr>
<td>12 years–adult</td>
<td>(250/125) 2 tabs</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 250/125 and 500/125 mg tablets, 250/125 dispersible tablets, 125 mg/5 ml, 250 mg/5 ml suspensions.

**Side-effects**
- Gastro-intestinal disturbances.

**Notes**
- Contains a penicillin. Monitor liver function in patients with pre-existing liver disease.

### Doxycycline orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 years</td>
<td>Contra-indicated</td>
<td></td>
</tr>
<tr>
<td>&gt;12 years and adult</td>
<td>200 mg on first day then 100–200 mg</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 50 and 100 mg capsules, 100 mg dispersible tablets.

**Side-effects**
- Gastro-intestinal disturbances, hepatotoxicity, blood disorders, hypersensitivity reactions.

**Notes**
- Avoid exposure to sunlight or sun lamps.

### Cefaclor orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–1 year</td>
<td>125 mg</td>
<td>8 hourly</td>
</tr>
<tr>
<td>1–7 years</td>
<td>250 mg</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Over 7 years &amp; adult</td>
<td>500 mg</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 500 mg capsules, 125 mg/5 ml, 250 mg/5 ml suspensions (375 mg modified release tablets for twice daily dosing).

**Administration**
- Take modified release tablets with or after food. Absorption of capsules and suspension is not affected by food.

**Side-effects**
- Diarrhoea, nausea and vomiting, headache, allergic reactions and blood dyscrasias.
Cefixime orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months–1 year</td>
<td>75 mg</td>
<td>24 hourly</td>
</tr>
<tr>
<td>1–5 years</td>
<td>100 mg</td>
<td>24 hourly</td>
</tr>
<tr>
<td>5–10 years</td>
<td>200 mg</td>
<td>24 hourly</td>
</tr>
<tr>
<td>Over 10 years &amp; adult</td>
<td>400 mg</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

Preparations: 200 mg tablets, 100 mg/5 ml suspension.
Side-effects: Similar to cefaclor (above).
Notes: Reduce dose in renal impairment. Reserved for resistant *H. influenzae* infections.

8.5 Treatment of severe exacerbations of *Haemophilus influenzae* infection

Chloramphenicol orally (section 4.8)

Although *H. influenzae* is usually sensitive to chloramphenicol, in most cases the organism is also sensitive to a range of other antibiotics, which do not carry the risk of severe aplastic anaemia seen (rarely) with chloramphenicol. There are anecdotal reports of the use of chloramphenicol for infection with *P. aeruginosa* and *B. cepacia* complex.

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &amp; Adult</td>
<td>12.5–25 mg/kg Higher dose for severe infections – reduce as soon as indicated.</td>
<td>6 hourly</td>
</tr>
</tbody>
</table>

Preparations: 250 mg capsules, liquid available as a special.
Side-effects: Blood disorders including aplastic anaemia. Monitor blood counts before and during treatment. Avoid, if possible, in renal or hepatic impairment. Also gastrointestinal disturbances, peripheral and optic neuritis.
Notes: Also active against most *S. aureus*.

Cefuroxime intravenously

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>50 mg/kg (max 1.5 g)</td>
<td>6–8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>750 mg–1.5 g</td>
<td>6–8 hourly</td>
</tr>
</tbody>
</table>

Preparations: 250 mg, 750 mg and 1.5 g vial.
Administration: Slow intravenous injection.
Side-effects: Similar to cefaclor (section 8.4).
Notes: Reduce dose in renal impairment – see specialist texts.
Cefotaxime intravenously

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>50 mg/kg (max 12 g in 24 hours)</td>
<td>6–8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>2 g (max 12 g in 24 hours)</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

Preparations: 500 mg, 1 g and 2 g vials.

Administration: Slow intravenous injection over 3–4 minutes.

Side-effects: Similar to cefaclor (section 8.4).

Notes: Reduce dose in renal impairment. Less active against S. aureus than cefuroxime.

8.6 Treatment of atypical infection e.g. Mycoplasma & Non-tuberculous mycobacteria (section 7.8.3)

Clarithromycin orally (for *Mycobacterium avium* complex – MAC)
and intravenously (*M. abscessus*)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 years orally</td>
<td>7.5 mg/kg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult orally</td>
<td>500 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>1 month–12 years intravenously</td>
<td>7.5 mg/kg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult intravenously</td>
<td>500 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

Preparations: 250 mg and 500 mg tablets, 125 mg/5 ml and 250 mg/5 ml suspensions, 125 mg, 187.5 mg and 250 mg straws, 250 mg sachets, 500 mg vials.

Administration: Give intravenous over 60 minutes.

Side-effects: Gastrointestinal upset and allergic reactions.

Notes: Caution in hepatic or renal impairment. Interacts with a variety of other drugs including theophylline, cimetidine and immunosuppressants. Doses may be doubled in e.g., NTM.

Azithromycin for *Mycobacterium avium* complex (MAC)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months–18 years</td>
<td>10 mg/kg (max 500 mg)</td>
<td>Once daily</td>
</tr>
<tr>
<td>Adult</td>
<td>500 mg</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

Preparations: 250 mg capsules, 250 mg and 500 mg tablets, 200 mg/5 ml suspension.

Administration: Take capsules on an empty stomach. Do not take indigestion remedies at the same time.

Side-effects: Gastrointestinal upset and allergic reactions.

Notes: Resistance can occur with repeated courses. Fewer drug interactions than erythromycin. Also used as an anti-inflammatory (sections 4.10 & 8.10).
Rifampicin (MAC) See section 8.2 for preparation, administration side effects and notes. In MAC infection rifampicin is administered 24 hourly.

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–12 years</td>
<td>10 mg/kg</td>
<td>24 hourly</td>
</tr>
<tr>
<td>&gt;12 years &amp; adult &lt;50 kg</td>
<td>450 mg od</td>
<td>24 hourly</td>
</tr>
<tr>
<td>&gt;12 years &amp; adult ≥50kg</td>
<td>600 mg od</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

Ethambutol (MAC)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>15 mg/kg (max 1.5 g)</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

Preparations: 500 mg, 1 g and 2 g vials.
Administration: Slow intravenous injection over 3–4 minutes.
Side-effects: Similar to cefaclor (section 8.4).
Notes: Reduce dose in renal impairment. Less active against S.aureus than cefuroxime.

Cefoxitin (M.abscessus)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &lt;12 years</td>
<td>40 mg/kg</td>
<td>6 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>2–3 g</td>
<td>6 hourly</td>
</tr>
</tbody>
</table>

Preparations: 1 g and 2 g vials.
Administration: Slow iv injection or infusion over 30 minutes.
Side-effects: Gastro-intestinal effects, hypersensitivity reactions.
Notes: Not available in the UK, may be imported on a named patient basis. Can interfere with some laboratory tests for creatinine.

Nebulised Amikacin (for intravenous dosing see section 8.8)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &lt;12 years</td>
<td>250 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>500 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

Preparations: 250 mg/ ml vial.
Administration: Make up to 4 ml with 0.9% sodium chloride.
Side-effects: Sensitivity reactions. Local effects.
Notes: Give first dose in hospital, can cause bronchospasm, monitor lung function before and after.
8.7 Treatment of *Pseudomonas aeruginosa* infection – first isolates or in chronically infected patients who have a mild exacerbation

A combination of oral ciprofloxacin and nebulised colistin is now widely used to eradicate early *P. aeruginosa* infection (section 5.2.2 for details).

**Ciprofloxacin orally**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–5 years orally</td>
<td>15 mg/kg</td>
<td>12 hourly</td>
<td>3 weeks–3 months for eradication. Usually 2 weeks for chronically infected patients</td>
</tr>
<tr>
<td>5–18 years orally</td>
<td>20 mg/kg (max 750 mg)</td>
<td>12 hourly</td>
<td></td>
</tr>
<tr>
<td>Adult orally</td>
<td>750 mg</td>
<td>12 hourly</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacokinetic data suggest that 8 hourly dosing may give more effective sputum concentrations in adults.\(^1\)

**Preparations**

100 mg, 250 mg, 500 mg and 750 mg tablets, 250 mg/5 ml suspension.

**Administration**

Do not take milk, indigestion remedies, iron or zinc preparations at the same time as oral preparations.

**Side-effects**

May induce convulsions – taking NSAIDS or theophylline at the same time increases the risk. Other side effects include nausea, vomiting, joint pain, abdominal pain, headache, rash, dizziness, pruritus, hepatitis and jaundice. Nausea commonly resolves with lower doses. A photosensitive skin erythema is relatively common – avoid exposure to strong sunlight. Discontinue if psychiatric, neurological or hypersensitivity reactions occur.

**Notes**

Use with caution in epileptic patients. Reduce dose in severe renal impairment. Interacts with a variety of other drugs including theophylline and NSAIDS. While ciprofloxacin does have activity against gram-positive infections, there is a high incidence of resistance in *S. aureus* after repeated dosing.

**Colistin inhaled**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Times daily</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>All</td>
<td>1 million units</td>
<td>2</td>
</tr>
<tr>
<td>Step 2</td>
<td>All</td>
<td>1 million units</td>
<td>3</td>
</tr>
<tr>
<td>≥2y</td>
<td>All</td>
<td>2 million units</td>
<td>3</td>
</tr>
<tr>
<td>Step 3</td>
<td>All</td>
<td>1 million units</td>
<td>3</td>
</tr>
<tr>
<td>≥2y</td>
<td>All</td>
<td>2 million units</td>
<td>3</td>
</tr>
</tbody>
</table>

*Step 1 is given for the 1st respiratory isolate of *Paeruginosa*, step 2 for the 2nd and step 3 for ALL subsequent respiratory isolates. Many CF centres will give step 3 (3 months of treatment) from the first isolate of *Paeruginosa*.\(^3\)

**Preparations**

500,000 unit, 1 million unit and 2 million unit vials.

**Administration**

Details in sections 5.10.1 and 5.10.2.

**Side-effects**

Bronchospasm – may be prevented by an inhaled bronchodilator. The tendency to bronchoconstriction can be reduced by the use of a more isotonic solution. Transient sensory disturbances.

**Notes**

Give first dose in hospital and measure lung function before and after dose.
8.8 Treatment of early *Pseudomonas aeruginosa* infections not cleared by ciprofloxacin and colistin and of moderate and severe exacerbations of *Pseudomonas aeruginosa* infection

Please see section 6 for full discussion of intravenous antibiotic therapy.

8.8.1 Anti-pseudomonal penicillins

**Piperacillin - Tazobactam intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child</td>
<td>90 mg/kg (max 4.5 g)</td>
<td>6–8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>4.5 g</td>
<td>6–8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

2.25 g (piperacillin 2 g and tazobactam 250 mg) 4.5 g (piperacillin 4 g and tazobactam 500 mg) vials.

**Administration**

Intravenous injection over 3–5 minutes or infusion over 20–30 mins.

**Side-effects**

Hypersensitivity reactions, gastrointestinal reactions, blood dyscrasias.

**Ticarcillin - Clavulanic acid intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>80–100 mg/kg (max 3.2 g)</td>
<td>6–8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>3.2 g</td>
<td>6–8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

3.2 g (ticarcillin 3 g and clavulanic acid 200 mg) vial.

**Administration**

Intravenous infusion over 30–40 minutes.

**Side-effects**

Gastrointestinal upset, rash, hepatitis and cholestatic jaundice.

**Notes**

Reduce dosage in renal impairment. May be useful in *S.maltophilia* infection.

8.8.2 Third generation cephalosporins

**Ceftazidime intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>50 mg/kg (max 3 g) – Can be given in 2 doses (max 3 g / dose)</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>2–3 g</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

250 mg, 500 mg, 1 g, 2 g and 3 g vials.

**Administration**

Slow intravenous injection.

**Side-effects**

Rash, hypersensitivity reactions, diarrhoea, nausea and vomiting, headache.

**Notes**

Reduce dose in renal impairment. Continuous ceftazidime infusion is advocated by some centres.45
8.8.3 Other β-lactam antibiotics

These drugs can be used as second-line agents if hypersensitivity reactions have occurred following anti-pseudomonal penicillins or cephalosporins or the organism is resistant to 1st line therapy.

**Aztreonam intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–2 years</td>
<td>30 mg/kg</td>
<td>6–8 hourly</td>
</tr>
<tr>
<td>2–12 years</td>
<td>50 mg/kg (max 2 g)</td>
<td>6–8 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult</td>
<td>2 g</td>
<td>6–8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

500 mg, 1 g and 2 g vials.

**Administration**

Intravenous injection over 3–5 minutes.

**Side-effects**

Rash, blood dyscrasias, diarrhea, nausea, vomiting, jaundice and hepatitis.

**Notes**

Reduce dose in moderate to severe renal impairment. A narrow spectrum of activity against gram-negative pathogens including *H. influenzae*. No anti gram-positive activity, therefore usually used in combination with an aminoglycoside.

**Imipenem - Cilastatin intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child less than 40 kg</td>
<td>22.5 mg/kg</td>
<td>6 hourly</td>
</tr>
<tr>
<td>Child over 40 kg &amp; adult</td>
<td>1 g</td>
<td>6–8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

500 mg imipenem with 500 mg cilastatin.

**Administration**

Infuse 500 mg or less over 20–30 minutes, doses greater than 500 mg over 40–60 minutes.

**Side-effects**

Rash, nausea, and vomiting (may be helped by reducing infusion rate), blood dyscrasias, confusion, dizziness and seizures.

**Notes**

Use with caution in patients with central nervous system disorders. Reduce dosage or avoid in renal impairment.

**Meropenem intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>4–18 years</td>
<td>25–40 mg/kg (max 2 g)</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Child &gt;50 kg &amp; adult</td>
<td>1–2 g</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

500 mg and 1 g vials.

**Administration**

Intravenous injection over 5 minutes.

**Side-effects**

Skin reactions, gastrointestinal reactions, blood dyscrasias and headache.

**Notes**

Reduce dosage / frequency in renal impairment – see specialist texts. Antimicrobial activity as for imipenem (above). Useful in *B. cepacia* infections.
8.8.4 Polymyxins

Useful where there is hypersensitivity or *P. aeruginosa* is resistant to 1st line agents. Almost all *P. aeruginosa* are sensitive.

**Colistin intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child under 60 kg</td>
<td>25,000 units/kg</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Child over 60 kg &amp; adult</td>
<td>2,000,000 (2 million) units</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

500,000 unit, 1 million unit and 2 million unit vials.

**Administration**

Slow intravenous infusion.

**Side-effects**

Sensory disturbances, vasomotor instability, visual disturbance, confusion and neurotoxicity.

**Notes**

Reduce dosage in renal impairment and when used in combination with nephrotoxic drugs. Monitor renal function. The majority of *P. aeruginosa* are sensitive. Now frequently used in some units where resistance to other drugs is a problem.

8.8.5 Aminoglycosides

These are used in combination with other treatments (*sections 8.8.1 and 8.8.2*) and may have a synergistic effect with β-lactams. Consider hearing tests for those receiving repeated dosages. Tobramycin is recommended, as it is more active against *P. aeruginosa* than gentamicin (*section 6*).

**Tobramycin intravenously**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children &amp; adults</td>
<td>10 mg/kg (max 660 mg)</td>
<td>24 hourly</td>
</tr>
<tr>
<td></td>
<td>Some patients may find the 30 minute infusion inconvenient in which case 3 times daily dosing may be used.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.3 mg/kg</td>
<td>8 hourly</td>
</tr>
</tbody>
</table>

**Preparations**

40 mg, 80 mg and 240 mg vials.

**Administration**

Give once daily dose as infusion over 30 minutes, three times daily dose can be given as an intravenous injection over 3–5 minutes. Do not mix with other antibiotics in the same syringe.

**Side-effects**

Nephrotoxicity and ototoxicity.

**Notes**

Use previous treatment doses as a guide to starting doses in individual patients (if available). Ensure adequate hydration and normal renal function at the start of therapy. Reduce dosage in renal impairment. With extended interval dosing aim for a level 18 hours post dose of <1 mg/l, re-check after one week (some units check the level after 24 hours).

With three times daily dosing monitor blood levels after the 3rd or 4th dose and weekly thereafter if satisfactory. Aim for trough <1 mg/l and peak 8–12 mg/l (at 1 hr). Always discuss with local microbiologist, as routines for determining blood levels vary.

Also active against *S. aureus* and *H. influenzae*. 
### Amikacin intravenously

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–18 years</td>
<td>10 mg/kg (max 500 mg)</td>
<td>8 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>7.5 mg/kg (max 750 mg)</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**: 100 mg and 500 mg in 2 ml.

**Administration**: Slow intravenous injection.

**Side-effects**: Nephrotoxicity and ototoxicity.

**Notes**: Ensure adequate hydration and normal renal function at the start of therapy. Reduce dosage in renal impairment. Aim for trough level of <10 mg/l. Peak should not exceed 25 to 30 mg/l at 1 hr. Also used for *M. abscessus*.

### 8.8.6 Other intravenous antibiotics - Fosfomycin

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–12 years (10–40 kg)</td>
<td>100 mg/kg</td>
<td>8 hourly</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>5 g (total daily dose can be increased to 20g)</td>
<td>8–12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**: 2, 3 and 5 g vials available.

**Administration**: Intravenous infusion over 30 mins.

**Side-effects**: Can cause electrolyte disturbance.

**Notes**: Adjust dose in renal impairment. Not available in the UK. May be imported on a named patient basis.
8.9 Inhaled anti-pseudomonal antibiotics

There are currently three preparations licensed for the treatment of *P. aeruginosa* in cystic fibrosis, colistin (Colomycin® and Promixin®) and preservative free tobramycin solution for inhalation (TSI or TOBI®). Colistin is the drug of first choice for nebulised use as resistance rarely occurs even after prolonged use. In combination with oral ciprofloxacin it is the treatment of choice for early eradication of new *P. aeruginosa* infections (section 5.2.2). Nebulised colistin is widely used as long-term treatment for patients chronically infected with *P. aeruginosa* (section 5.3.2).

**Colistin inhaled**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month–2 years</td>
<td>500,000–1 million units</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Over 2 years &amp; adult</td>
<td>1–2 million units*</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
500,000 unit, 1 million unit and 2 million unit vials.

**Administration**
Details in sections 5.7 and 5.8.

**Side-effects**
Bronchospasm – may be prevented by an inhaled bronchodilator. The tendency to bronchoconstriction can be reduced by the use of a more isotonic solution. Transient sensory disturbances.

**Notes**
* Many CF centres use 1MU bd for children <2–10 years and 2MU bd for patients over 10 years. Give first dose in hospital and measure lung function before and after dose.

**Tobramycin inhaled**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over 6 years &amp; adult</td>
<td>300 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternating 28 days on and 28 days off</td>
</tr>
</tbody>
</table>

**Preparations**
Solution for inhalation 300 mg/5 ml preservative-free.

**Administration**
Details in section 5.

**Side-effects**
Voice alteration, local effects, and tinnitus.

**Notes**
Give first dose in hospital and measure lung function before and after dose.
### 8.10 Chronic oral anti-pseudomonal therapy

**Azithromycin**

(There is accumulating evidence that azithromycin may also be beneficial, as long term therapy, in CF patients who do not have chronic infection with *P. aeruginosa*.)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 kg</td>
<td>250 mg</td>
<td>Daily three times a week</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>500 mg</td>
<td>Daily three times a week</td>
</tr>
</tbody>
</table>

**Preparations** 250 mg capsules, 250 mg and 500 mg tablets 200 mg/5 ml suspension.

**Administration** Take capsules on an empty stomach. Do not take indigestion remedies at the same time.

**Side-effects** Gastrointestinal upset and allergic reactions.

**Notes** Review after 6 months. Fewer drug interactions than erythromycin.

### 8.11 Drugs used in the treatment of *Burkholderia cepacia* infections

It is advisable to discuss the occurrence, treatment and general management of patients considered to be infected with *B. cepacia* with a microbiologist experienced in this pathogen.

**Co-trimoxazole orally**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks–6 months</td>
<td>120 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>6 months–6 years</td>
<td>240 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>6–12 years</td>
<td>480 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult</td>
<td>960 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 480 mg and 960 mg tablets, 240 mg/5 ml and 480 mg/5 ml suspensions.

**Side-effects** Gastrointestinal disorders, rash (discontinue immediately), blood disorders (discontinue immediately), jaundice, Stevens-Johnson syndrome.

**Notes** Caution in hepatic or renal impairment. Also active against *S. aureus* and *H. influenzae* and useful in *S. maltophilia* infections ([section 7.3](#)).

**Trimethoprim orally**

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 month–12 year</td>
<td>4 mg/kg (max 200 mg)</td>
<td>12 hourly</td>
</tr>
<tr>
<td>Over 12 years &amp; adult</td>
<td>200 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 100 mg, 200 mg, 50 mg/5 ml suspension.

**Side-effects** Gastrointestinal disorders, hypersensitivity reaction, blood disorders (discontinue immediately).
Doxycycline orally

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–18 years (contraindicated &lt;12 years)</td>
<td>200 mg on first day then 100–200 mg</td>
<td>24 hourly</td>
</tr>
<tr>
<td>Adult</td>
<td>200 mg</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

Preparations: 50 mg and 100 mg capsules, 100 mg dispersible tablets.

Administration: Swallow capsule whole with plenty of water while sitting or standing. Do not take indigestion remedies, iron or zinc preparations at the same time. Avoid exposure of skin to direct sunlight or sunlamps.

Side-effects: Gastrointestinal disorders, erythema (discontinue treatment), headache and visual disturbances, hepatotoxicity.

Notes: Also active against most *H. influenzae* and some *S. aureus*.

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8.12 Treatment of more severe *Burkholderia cepacia* infection (section 7.1.1)

Ceftazidime - details in section 8.8.2.

Meropenem - details in section 8.8.3.

Imipenem - details in section 8.8.3.

Piperacillin-tazobactam - details in section 8.8.1

Co-trimoxazole intravenously

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mths–6 years</td>
<td>240 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>6–12 years</td>
<td>480 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>960 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

Preparations: 480 mg in 5 ml; 960 mg in 10 ml.

Administration: Dilute in 0.9% sodium chloride or 5% dextrose.
240 mg = 2.5 ml in 62 ml diluent.
480 mg = 5 ml in 125 ml diluent.
960 mg = 10 ml in 250 ml diluent.
Intravenous infusion over 60 minutes.

Side-effects: Blood disorders, Nausea.

Notes: Caution in hepatic or renal impairment. Can increase dose by 50% in severe infection.
### Temocillin

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;12 years (&gt;&amp;45 kg)</td>
<td>1–2 g</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**: 1 g vials.

**Administration**: Intravenous injection over 3–4 minutes.

**Side-effects**: Hypersensitivity reactions, blood disorders.

**Notes**: Not active against P. aeruginosa.

### 8.13 Use of nebulised antimicrobials in chronic *Burkholderia cepacia* infection

#### Ceftazidime inhaled

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &amp; adult</td>
<td>1 g</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**: 250 mg, 500 mg, 1 g, 2 g and 3 g vials.

**Administration**: Dissolve in 3 ml water for injection.

**Side-effects**: Sensitivity reactions. Local effects.

**Notes**: Give first dose in hospital, can cause bronchospasm, monitor lung function before and after.

#### Taurolidine inhaled

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>4 ml of 2% solution</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**: 2% solution. 5 ml ampoules or 250 ml vials.

**Administration**: section 5.8.

**Side-effects**: Sensitivity reactions. Local effects.

**Notes**: Give first dose in hospital, can cause bronchospasm, monitor lung function before and after. Taurolidine is not licensed for this indication.
### 8.14 Anti-fungal treatment

#### Itraconazole

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>All – oral</td>
<td>5 mg/kg (max 400 mg)</td>
<td>24 hourly or 12 hourly if dose exceeds 200 mg</td>
</tr>
</tbody>
</table>

**Preparations**
- 50 mg/5 ml oral liquid, 100 mg capsules.

**Administration**
- Take liquid on an empty stomach and do not eat for 1 hour afterwards; take capsules immediately after a meal. If patient is on a proton pump inhibitor or H2 antagonist they should be advised to take the dose with a cola (or similar) drink.

**Side-effects**
- Gastro-intestinal effects, jaundice, hepatitis, heart failure, pulmonary oedema, headaches and dizziness.

**Notes**
- Monitor levels in patients who fail to respond and adjust dose accordingly. Take levels 2 hours post dose.

#### Voriconazole

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–12 years</td>
<td>200 mg</td>
<td>12 hourly</td>
</tr>
<tr>
<td>&gt;12 years and &lt;40 kg</td>
<td>200 mg, 100 mg</td>
<td>12 hourly for 2 doses then 12 hourly</td>
</tr>
<tr>
<td>&gt;12 years and &gt;40 kg</td>
<td>400 mg, 200 mg</td>
<td>12 hourly for 2 doses then 12 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- 50 mg and 200 mg tablets, 200 mg/5 ml suspension.

**Administration**
- Take on an empty stomach.

**Side-effects**
- Gastrointestinal disturbances, blood disorders, visual disturbances, photosensitivity, jaundice and renal failure.

**Notes**
- Doses may be increased to 150 mg bd (>12 years and >40 kg) and 300 mg bd (>12 years and >40 kg) if necessary.

#### Fluconazole (for systemic candidiasis or infection of indwelling intravenous access device)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mth–18 years</td>
<td>6–12 mg/kg (max 400 mg)</td>
<td>24 hourly</td>
</tr>
<tr>
<td>Adults</td>
<td>400 mg</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

**Preparations**
- Vials: 100 mg in 50 ml, 200 mg in 100 ml, & 400 mg in 200 ml.

**Administration**
- IV over 10–30mins maximum rate 5–10 ml/min.

**Side-effects**
- Abnormal liver function. Exfoliative dermatitis has been reported.

**Notes**
- The IV & oral doses are the same but if attempting to treat infection in an intravenous access device, then fluconazole should be administered IV, through the device.
Liposomal Amphotericin ("Ambisome") - for systemic candidiasis or infection of indwelling intravenous access device

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>100 microgram/kg (max 1 mg)</td>
<td>Test dose</td>
</tr>
<tr>
<td></td>
<td>1 mg/kg</td>
<td>24 hourly day 1</td>
</tr>
<tr>
<td></td>
<td>2 mg/kg</td>
<td>24 hourly day 2</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg</td>
<td>24 hourly to continue</td>
</tr>
</tbody>
</table>

**Preparations** 50 mg vials.

**Administration** Reconstitute each vial with 12 ml water for injection and shake vigorously this gives 4 mg/ml. Dilute the required dose in glucose 5% via the filter provided to a final concentration of 0.2–2 mg/ml. Infuse over 30–60 minutes.

**Side-effects** Sensitivity reactions. Electrolyte disturbances.

**Notes** Can increase to a maximum dose of 5 mg/kg. If attempting to treat infection in an intravenous access device, then amphotericin should be administered IV through the device.

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Caspofungin

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2–18 years</td>
<td>70 mg/m2 (max 70 mg) loading dose then 50 mg/m2 (max 70 mg)</td>
<td>24 hourly</td>
</tr>
<tr>
<td>Adult &lt;80 kg</td>
<td>70 mg loading dose then 50 mg daily</td>
<td>24 hourly</td>
</tr>
<tr>
<td>Adult ≥ 80 kg</td>
<td>70 mg daily</td>
<td>24 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 50 mg and 70 mg vials.

**Administration** IV over 60 mins. Do not reconstitute in fluids containing glucose.

**Side-effects** Phlebitis, fever, abnormal liver and renal function, hypokalaemia, hypomagnesaemia. Anaphylaxis has been reported.

**Notes** Caution in hepatic impairment.

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8.15 Treatment of *Stenotrophomonas maltophilia* (section 7.3)

Co-trimoxazole (section 8.11 & 8.12)

Tigecycline

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>100 mg</td>
<td>Initial dose</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>50 mg</td>
<td>12 hourly</td>
</tr>
</tbody>
</table>

**Preparations** 50 mg vials.

**Administration** Dilute to 100 ml and give over 30–60 minutes.

**Side-effects** Nausea and vomiting, dizziness, headache, sensitivity reactions.

**Notes** Nausea may be severe, pre-medicate with an anti-emetic.
8.16 References


9. ANTIBIOTIC-RELATED ALLERGIES AND DESENSITISATION

Patients with CF are at risk of developing allergic reactions to antibiotics because of repeated high dose intravenous drug administration. The choice of antibiotics may be limited by a history of previous allergic reaction and patients may thus be denied optimal treatment.

9.1 Extent of the problem

Hypersensitivity reactions are reported with most of the antibiotics in regular use for patients with CF including aminoglycosides, semisynthetic penicillins, other β-lactams, and quinolones. In one study of 121 patients with CF 75 (62%) experienced 125 reactions, those to piperacillin being most frequent (50.9%) and aztreonam the least common. In another series, 18 of 53 patients with CF experienced a reaction including 33% of patients treated intravenously and 9.5% of all IV courses: once again piperacillin was the most allergenic antibiotic. Seventy-one of 196 (36%) adults with CF experienced one or more antibiotic hypersensitivity reaction.

9.2 Desensitisation

The idea of using a desensitisation method to prevent recurrence of allergic reaction in patients with CF is well established. The regimen involves administration of a 10⁻⁶ times dilution of the drug followed by 6 ten-fold increases in the concentration until the therapeutic dose is given. Each dilution is infused consecutively over 20 minutes. During the desensitisation procedure, which takes about 2–3 hours, the patient is observed for signs of allergy. If 7 infusions are tolerated, the therapeutic dose is continued until the course is completed. In one series, 54 of 61 desensitisation procedures were successful.

Desensitisation must be repeated in full for each course of treatment, and during any course of therapy, if more than 1 day’s doses are omitted. If any of the escalating desensitisation doses is not tolerated the process is abandoned and not repeated on that occasion.

9.3 Recommendations

- Example of a desensitisation regimen in an adult
  - ceftazidime 0.004 mg in 50 ml sodium chloride 0.9% [NaCl]
  - ceftazidime 0.04 mg in 50 ml NaCl
  - ceftazidime 0.4 mg in 50 ml NaCl
  - ceftazidime 4 mg in 50 ml NaCl
  - ceftazidime 40 mg in 50 ml NaCl
  - ceftazidime 400 mg in 50 ml NaCl
  - ceftazidime 4,000 mg in 50 ml NaCl.

- Each dose is infused consecutively over 20 minutes. If there is no adverse reaction the next dose follows at once.

- Adrenaline, hydrocortisone and an antihistamine should be readily available and the appropriate doses for the patient known before starting the procedure.
• **Facilities for full resuscitation should be close at hand**. [C]

Desensitisation for hypersensitivity to other antibiotics has been carried out successfully. Successful desensitisation to tobramycin is reported where, interestingly, the tolerance was later maintained by the use of long-term nebulised tobramycin.¹ [IV] Other reports of desensitisation include ciprofloxacin,⁴ [IV] and patients with multiple allergic reactions to both β-lactams and aminoglycosides.⁷ [IV]

### 9.4 References

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