ANTIBIOTIC TREATMENT FOR CYSTIC FIBROSIS

CYSTIC FIBROSIS TRUST

Report of the UK Cystic Fibrosis Trust Antibiotic Group

September 2002

Second Edition

The Cystic Fibrosis Trust Antibiotic Group

CYSTIC FIBROSIS TRUST

11 London Road
Bromley
Kent BR1 1BY
Tel: 020 8464 7211
Fax 020 8313 0472
enquiries@cftrust.org.uk
www.cftrust.org.uk

© Cystic Fibrosis Trust 2002

ANTIBIOTIC TREATMENT FOR CYSTIC FIBROSIS

CONTENTS

9. PHARMACOPOEIA

10. ANTIBIOTIC–RELATED ALLERGIES AND DESENSITISATION

Grading scheme for recommendations used in the *Antibiotic Treatment for Cystic Fibrosis*

The criteria for the grading of recommendations in this document are based upon a paper by Petrie et al published on behalf of the Scottish Intercollegiate Guidelines Network.

Levels of evidence

Level	Type of evidence (based on AHCPR, 1992)
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well designed controlled study without randomisation.
IIb	Evidence for at least one other type of quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of recommendations

Grade	Type of recommendation (based on AHCPR, 1992)
A (levels Ia, Ib)	Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of the recommendation.
C (level IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Petrie GJ, Barnwell E, Grimshaw J, on behalf of the Scottish Intercollegiate Guidelines Network. *Clinical guidelines: criteria for appraisal for national use.* Edinburgh: Royal College of Physicians, 1995.

Agency for Health Care Policy and Research. *Acute pain management, operative or medical procedures and trauma 92-0032. Clinical practice guidelines.* Rockville, Maryland, USA: Agency for Healthcare Policy and Research Publications, 1992.

1. THE USE OF ANTIBIOTICS IN CYSTIC FIBROSIS

1.1 Introduction

The main objective when treating people who have cystic fibrosis (CF) is to prevent, eradicate or control all types of respiratory infection, particularly endobronchial and pulmonary infection with *Staphylococcus aureus*, *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Burkholderia cepacia*. The common viral respiratory infections are important in initiating and exacerbating the chest infection and contribute to the associated damaging inflammatory process. It is important that people who have CF receive the usual immunisations particularly against whooping cough and measles and have annual protection against influenza.

Without antibiotic treatment, the abnormal respiratory secretions of the infant with CF soon become infected (Armstrong et al, 1996 [III]); endobronchial infection and inflammation become established and eventually progress to fatal respiratory failure. However, there are striking differences in the prevalence rates for all types of infection in patients attending different CF clinics and these are almost certainly determined by local differences in preventive measures and treatment policies (Bauernfeind et al, 1996 [IV]). *This suggests that, at least for a proportion of patients, endobronchial infection is not inevitable.*

Recent reports of a highly transmissible *P. aeruginosa* affecting a number of patients with CF in the same Specialist CF Centre (Jones et al, 2001 [IV]; McCallum et al, 2001 [IV]) have heightened the need for strict hygienic precautions, regular expert microbiological monitoring and in some instances the introduction of patient segregation according to microbiological status (*A statement on <u>Burkholderia cepacia</u>*. Cystic Fibrosis Trust, 1999 [IV]; *<u>Pseudomonas aeruginosa</u> infection in people with cystic fibrosis*. Cystic Fibrosis Trust, 2001 [IV]).

1.2 Present day antibiotic regimens are increasingly effective in cystic fibrosis

It is now established that various regimens of oral, nebulised and intravenous antibiotics can prevent, eradicate or delay chronic infection of the lower airways (Valerius et al, 1991 [Ib]; Weaver et al, 1994 [Ib]; Frederiksen et al, 1997 [IIb]; Ratjen et al, 2001 [IIb]). Even when airway infection becomes established, the decline of respiratory function can be slowed by appropriate antibiotic treatment.

1.3 Use of antibiotics in CF differs from their use in unaffected individuals

The general approach to treat aggressively any pathogens isolated differs from that for the general population and often requires higher doses for longer periods compared with non-CF individuals. In non-CF individuals most respiratory infections will resolve completely without antibiotics. In contrast, in CF, chronic and progressive lower respiratory tract infection is early and inevitable, leading to death in early childhood, unless antibiotic treatment is used.

As lower respiratory infection is often difficult to identify from upper respiratory cultures, antibiotics are often given on the strong probability of there being a susceptible chest infection.

1.4 Particular problems when using antibiotics in people with cystic fibrosis

The metabolism and clearance rate of some antibiotics are altered in individuals with CF and also varies with the severity of the chest infection (Sorgel et al, 1996 [III]). The doses required and plasma levels achieved are different in people with CF from other patients. The need to use repeated courses of potentially toxic drugs, such as aminoglycosides, over many years increases the

need for careful monitoring to prevent impairment of renal function, hearing and other adverse effects. With repeated exposure to the same antibiotics, hypersensitivity reactions are more likely to occur and, in one series, affected over 60% of patients (Koch et al, 1991 [IV]). The frequent use of antibiotics to treat chronic infection increases the risk of bacterial resistance and the need for regular expert microbiological monitoring (Saiman & Prince, 1996 [IV]; Kenwood et al, 2001 [IV]).

Implantable venous access devices are valuable when venous access is difficult and may improve the patient's quality of life. The introduction of home intravenous (IV) antibiotic therapy has been a major factor in improving the prognosis and daily lives of many patients with cystic fibrosis. The CF Nurse Specialist has a key role in implementing many of these complex treatment regimes, such as home IV therapy. All patients should have access to a Specialist CF Nurse when self-treating at home (*National Consensus Standards for the Nursing Management of Cystic Fibrosis. UK Cystic Fibrosis Nurse Specialist Group.* Cystic Fibrosis Trust, 2001 [IV]).

1.5 Health and survival are clearly related to the presence, severity and progress of the chest infection

Although the present median survival of over 30 years for patients with CF is vastly better than a decade ago, it is poor when compared to that of unaffected individuals. The main cause of death is respiratory failure secondary to chronic pulmonary infection. In the majority of patients this infection is first acquired in early childhood. Every year improved treatment is reflected in the improved survival figures (Dodge et al, 1997 [III]). Although many factors have contributed to the improved prognosis, survival is clearly better among those who do not have chronic chest infection. Recently in the USA, if respiratory cultures remained negative (suggesting that bacterial infection was absent), the average survival was 39 years, but if the patient is chronically infected with *P. aeruginosa*, average survival was only 28 years and, if infected by *B. cepacia*, only 16 years (Cystic Fibrosis Foundation Patient Registry, 1996 [III]). It is now well established that progress is worse when chronic infection with *P. aeruginosa* becomes established (Kerem et al, 1990 [III]; Pamukcu et al, 1995 [III]; Nixon et al, 2001 [III]). Although a slow steady decline of respiratory function with age is seen in cross-sectional data, respiratory function remains stable for many years in individuals who avoid chronic infection.

1.6 The prevalence of chronic infection differs between Specialist CF Centres

The prevalence of the respiratory pathogens recovered from people with CF differs considerably between clinics, possibly reflecting different infection control and antibiotic treatment policies. There are considerable differences in the way antibiotics are used for people with CF in the UK, even between large Specialist CF Centres (Taylor et al, 1993 [IV]) and even greater differences amongst countries (Bauernfeind et al, 1996 [IV]).

1.7 Early treatment is more successful in achieving eradication

The introduction of neonatal screening for CF and diagnosis within the first weeks of life allows an early start to preventive measures, regular microbiological monitoring for the presence of respiratory infection, and early antibiotic treatment. Chronic *S. aureus* and chronic *P. aeruginosa* are impossible to eradicate once well established; but, if treated early, both *S. aureus* (Szaff & Hoiby, 1981 [IV]) and *P. aeruginosa* (Littlewood et al, 1985 [IV]; Valerius et al, 1991 [Ib]; Brett et al, 1992 [IIb]; Frederiksen et al, 1997 [IIb]; Doring et al, 2000 [IV]) can be cleared successfully.

1.8 Conclusion

Antibiotics are one of the most important components of present-day CF treatment, which has

been responsible for an increase in the median survival from 2 years to over 30 years. The quality of life, length of survival and the cost of care are commonly determined by the success or otherwise of the antibiotic treatment of the initial *P. aeruginosa* infection in early childhood, and by the subsequent antibiotic treatment.

In an attempt to determine the best way to generalise such treatment regimens and to ensure that all people with CF benefit from them, the Cystic Fibrosis Trust organised this Antibiotic Group. The views set out in this Report are those agreed by this panel of experts. However, the recommendations are not mandatory guidelines, and the staff at individual Specialist CF Centres will wish to interpret them in the light of their own experience and perceived needs of each patient on a day-to-day basis.

We hope this second 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 cystic fibrosis.

1.9 References

Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage and oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol 1996; 21:267-275.

Bauernfeind A, Marks MI, Strandvik B, editors. Cystic Fibrosis Pulmonary Infections: Lessons from Around the World. Basel, Boston, Berlin: Birkhauser Verlag, 1996.

Brett MM, Simmonds EJ, Ghoneim AT, Littlewood JM. The value of serum IgG titres against *Pseudomonas aeruginosa* in the management of early pseudomonal infection in cystic fibrosis. Arch Dis Child 1992; 67:1086-1088.

Cystic Fibrosis Trust. National Consensus Standards for the Nursing Management of Cystic Fibrosis. UK Cystic Fibrosis Nurse Specialist Group. 2001.

Cystic Fibrosis Trust's Infection Control Group. A statement on *Burkholderia cepacia*. 1999.

Cystic Fibrosis Trust's Infection Control Group. *Pseudomonas aeruginosa* infection in people with cystic fibrosis. Suggestions for prevention and control. 2001.

Cystic Fibrosis Foundation, Patient Registry 1996 Annual Data Report, Bethesda, Maryland, August 1997.

Dodge JA, Morison S, Lewis PA, Coles EC, Geddes D, Russell G, et al. Incidence, population and survival of cystic fibrosis in the UK, 1968-1995. Arch Dis Child 1997; 77:493-496.

Doring G, Conway SP, Heijerman HGM, Hodson M, Hoiby N, Smyth A, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: A European Consensus. Eur Respir J 2000; 16:749-767.

Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonisation with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol 1997; 23:330-335.

Jones AM, Govan JRW, Doherty CJ, Dodd ME, Isalska BJ, Stanbridge TN, et al. Spread of a multiresistant strain of *Pseudomonas aeruginosa* in an adult cystic fibrosis clinic. Lancet 2001; 358:557-558.

Kenwood CJ, Livermore DM, James D, Warner M and the Pseudomonas Study Group. Antimicrobial susceptibility of *Pseudomonas aeruginosa*: results of a UK survey and evaluation of the British Society for Antimicrobial Chemotherapy disc susceptibility test. J Antimicrob Chemother 2001; 47:789-799.

Kerem E, Corey M, Gold R, Levison H. Pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonisation with *Pseudomonas aeruginosa*. J Pediatr 1990; 116:714-719.

Koch C, Hjelt K, Pedersen SS, Jensen ET, Jensen T, Lanng S, et al. Retrospective clinical study of hypersensitivity reactions to aztreonam and six other beta-lactam antibiotics in cystic fibrosis patients receiving multiple treatment courses. Rev Infect Dis 1991; 13 (Suppl 7):S608-S611.

Littlewood JM, Miller MG, Ghoneim AG, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet 1985; i :865.

McCallum SJ, Corkill J, Gallagher M, Ledson MJ, Hart CA, Walshaw MJ. Superinfection with a transmissible strain of *Pseudomonas aeruginosa* in adults with cystic fibrosis chronically colonised by *P. aeruginosa*. Lancet 2001; 358:558-560.

Nixon GM, Armstrong DS, Carzino R, Carlin JB, Olinsky A, Robertson CF, et al. Clinical outcome after early *Pseudomonas aeruginosa* infection in cystic fibrosis. J Pediatr 2001; 138:699-704.

Pamukcu A, Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonisation on lung function and anthropomorphic variables in children with cystic fibrosis. Pediatr Pulmonol 1995; 19:10-15.

Ratjen F, Doring G, Nikolaizik W. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. Lancet 2001; 358:983-984.

Saiman L, Prince A. Microbial resistance. In: Bauernfeind A, Marks MI, Strandvik B, editors. Cystic Fibrosis Pulmonary Infections: Lessons from Around the World. Basel, Boston, Berlin: Birkhauser Verlag, 1996:51-64.

Sorgel F, Kinzig M, Labisch C, Hofman M, Stephan U. Pharmacokinetics of antibacterials in cystic fibrosis. In: Bauernfeind A, Marks MI, Strandvik B, editors. Cystic Fibrosis Pulmonary Infections: Lessons from Around the World. Basel, Boston, Berlin: Birkhauser Verlag, 1996:13-27.

Szaff M, Hoiby N. Antibiotic treatment of *Staphylococcus aureus* infection in cystic fibrosis. Monogr Paediatr 1981; 14:108-114

Taylor RF, Hodson ME. Cystic fibrosis prescribing practices in the United Kingdom and Eire. Respir Med 1993; 87:535-539.

Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis by early treatment. Lancet 1991; 338:725-726.

Weaver LT, Green MG, Nicholson K, Mills J, Heeley ME, Kuzemko JA, et al. Prognosis of cystic fibrosis treated with continuous flucloxacillin from the neonatal period. Arch Dis Child 1994; 70:84-89.

2. MICROBIOLOGY AND ANTIBIOTIC THERAPY: A CF PERSPECTIVE

2.1 Introduction

Uncertainty continues as to the best antibiotic regimens at particular stages of CF disease. Moreover, the prevalence of multiresistant pathogens is increasing, reducing the efficacy of some therapies. It is therefore timely to consider the optimal antibiotic regimens for treating patients with CF in the light of present knowledge.

2.2 Bacterial pathogens

From birth, individuals with CF are susceptible to microbial infections of the major airways. The biological mechanisms underlying this susceptibility originate from the pathophysiological consequences of defective CFTR (cystic fibrosis transmembrane regulator). Viral infections increase susceptibility to the more important bacterial infections (Armstrong et al, 1998 [III]).

The spectrum of CF pathogens remains surprisingly limited (Gilligan, 1991 [III]; Govan & Deretic, 1996 [III]; Hutchinson & Govan, 2000 [III]). The classic sequence is age-related and consists of *S. aureus* in early infancy, followed by *H. influenzae* and *P. aeruginosa*. During the last decade, the *B. cepacia* complex (LiPuma, 1998 [III]) has emerged as a major pathogen in CF, and the possible role of *Stenotrophomonas maltophilia* awaits clarification (Denton & Kerr, 1998 [III]). *Burkholderia cepacia* has become a particular problem because of its multiresistance and the transmissibility of some strains. In approximately one-third of infected patients the organism causes 'cepacia syndrome', a fulminating pneumonia and septicaemia that can be swiftly fatal.

2.3 'Colonisation' versus 'infection'

Some microbiologists and clinicians describe asymptomatic carriage as merely 'colonisation' and retain the term 'infection' to describe periods of active exacerbation or clinical decline. Recently, however, analyses of bronchoalveolar lavage fluids from infants with CF revealed that inflammatory markers might be present in the lung from a very early age, with or without culture of known pathogens. Therefore, in this document, we shall apply the term 'infection' to describe culture of known pathogens from the respiratory tract. Infections often involve strains and species that vary over time in their antibiotic susceptibility: this behaviour is particularly seen for *P. aeruginosa* (Seale et al, 1979 [III]; Thomassen et al, 1979 [III]; Govan et al, 1987 [III]) and *B. cepacia* (Hobson et al, 1995 [III]; Pitt et al, 1996 [III]).

2.4 *Pseudomonas aeruginosa*

Pseudomonas aeruginosa remains the major pathogen of most patients with CF, the majority being initially chronically infected by their early teens. The classical non-mucoid form infects the airways prior to the subsequent emergence of the mucoid alginate-producing variants. The presence of the non-mucoid form is frequently asymptomatic and may be intermittent.

Eradication or major reduction of the bacteria in the early stages of colonisation is possible with appropriate antibiotic therapy (Littlewood et al, 1985 [IV]; Govan et al, 1987 [III]; Valerius et al, 1991 [Ib]; Frederiksen et al, 1997 [IIb]; Ratjen et al, 2001 [IIb]) thus reducing the microbial reservoir from which alginate-producing mutants later arise (Govan & Deretic, 1996 [III]). Once the transition to the mucoid form has occurred, infection becomes chronic and is associated with intermittent exacerbations and progressive lung disease. Antibiotic treatment of mucoid

P. aeruginosa infection may reduce the bacterial population in the sputum and produce some clinical benefit but permanent eradication is seldom if ever achieved. The molecular regulation of mucoidy in *P. aeruginosa* and the damaging consequences for the CF lung have recently been extensively reviewed (Govan & Deretic, 1996 [III]; Hutchinson & Govan, 2000 [III]).

Pseudomonas aeruginosa is inherently very resistant to antimicrobials, with low permeability, multiple drug efflux systems and a powerful chromosomal β-lactamase (Livermore, 1995 [III]; Nikaido, 1994 [III]). Further resistance arises via mutation or plasmid acquisition. Resistance rates to β-lactam, aminoglycoside and quinolone antibiotics are particularly high for isolates from patients with cystic fibrosis (Kenwood et al, 2001 [IV]). However, there are poor correlations between *in vitro* and *in vivo* behaviour of the *P. aeruginosa* which complicate susceptibility testing of isolates from patients with cystic fibrosis. Furthermore, definitions of resistance based on parental administration of antibiotics may not be relevant to aerosol delivery where concentrations 100-fold higher than systemic concentrations are achieved (Ramsay et al, 1999 [Ib]; Govan 2002 [IIb]). Some patients may carry multiple strains with different resistance profiles and, even when genomic fingerprinting shows infection by a single strain there is often considerable heterogeneity in the antibiogram within the infective population. Resistant subgroups may be selected during therapy (Denton & Wilcox, 1997 [III]), though these variants may have been too few in numbers to be detected in the initial susceptibility testing. Antimicrobial choices should be based on laboratory testing of a sample of colonial morphotypes rather than on a single colonial isolate (Wolter et al, 1995 [III]).

In vitro antimicrobial resistance is even greater in *B. cepacia* and *S. maltophilia* than in *P. aeruginosa*, and it is frequent to see isolates with apparent resistance to all antibiotics. *Burkholderia cepacia* presents a major problem, being increasingly associated with the spread of highly transmissible strains. These epidemic strains are variable in antibiogram, presumably reflecting the continuing accumulation of mutations or acquired DNA. However, the mechanisms and genetics of antimicrobial resistance in *B. cepacia* are unclear with the role of efflux, in particular, awaiting definition. The drugs most likely to remain active are co-trimoxazole, minocycline and meropenem (Pitt et al, 1996 [III]; Saiman, 1998 [III]; Nzula et al, 2002 [III]). The resistance mechanisms of *S. maltophilia* are better understood but *in vitro* data cannot easily be extrapolated into the patient, because the MICs of β-lactams and aminoglycosides vary widely with the susceptibility test conditions (Bonfiglio & Livermore, 1991 [III]; Wheat et al, 1985 [III]).

2.5 Summary

Antibiotic therapy for patients with CF requires a specialised approach that takes into account the idiosyncrasies of CF microbiology. During the past decade there have been significant improvements in the antimicrobial activity of antipseudomonal agents available and a growing acceptance of the microbiological rationale and clinical benefits of early and aggressive therapy against *P. aeruginosa* (Doring et al, 2000 [IV]). One of the most important advances is the discovery, from clinical trials, that chronic infection by mucoid *P. aeruginosa* can be reduced or delayed by early treatment with nebulised colomycin and oral ciprofloxacin (Littlewood et al, 1985 [IV]; Valerius et al, 1991 [Ib]; Frederiksen et al, 1997 [IIb]) or nebulised tobramycin (Ratjen et al, 2001 [IIb]). The rationale behind this strategy is that the virulent and intractable mucoid *P. aeruginosa* emerge as mutants from a reservoir of non-mucoid organisms. If treated early, these progenitor strains can be reduced or eliminated, delaying or even preventing the emergence of ineradicable mucoid variants (Govan et al, 1987 [III]; Govan & Deretic, 1996 [III]).

Even when early therapy fails to eradicate established mucoid *P. aeruginosa* infection, the use of agents such as tobramycin, ceftazidime, ciprofloxacin and meropenem results in reduced

inflammatory markers, improved lung function and an improved sense of wellbeing, associated with an improved clinical condition. Hypotheses to explain these benefits include reduction of the bacterial load in the CF lung (Govan et al, 1987 [III]; Regelman et al, 1990 [III]) and suppression of the biosynthesis of virulence factors, including alginate, which is a major pseudomonal virulence determinant in the context of cystic fibrosis (Govan & Deretic, 1996 [III]).

2.6 References

Armstrong D, Grimwood K, Carlin JB, Carzino R, Hull J, Olinsky A, et al. Severe viral respiratory infections in infants with cystic fibrosis. Pediatr Pulmonol 1998; 26:371-379.

Bonfiglio G, Livermore DM. Effect of media composition on the susceptibility of *Xanthomonas maltophilia* to β-lactam antibiotics. J Antimicrob Chemother 1991; 28:837-842.

Denton M, Wilcox MH. Antimicrobial treatment of pulmonary colonization and infection by *Pseudomonas aeruginosa* in cystic fibrosis patients. J Antimicrob Chemother 1997; 40:468-474.

Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. Clin Microbiol Rev 1998; 11:57-87.

Doring G, Conway SP, Heijerman HGH, Hodson M, Hoiby N, Smyth A, et al. Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis: A European Consensus. Eur Respir J 2000; 16:749-767.

Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonisation with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol 1997; 23:330-335.

Gilligan PH. Microbiology of airway disease in patients with cystic fibrosis. Clin Microbiol Revs 1991; 4:35-51.

Govan JRW, Doherty C, Glass S. Rational parameters for antibiotic therapy in patients with cystic fibrosis. Infection 1987; 15:300-307

Govan JRW, Deretic V. Microbial pathogenesis in cystic fibrosis: mucoid *Pseudomonas aeruginosa* and *Burkholderia cepacia*. Microbiol Rev 1996; 60:539-574.

Govan J R W. Insights into cystic fibrosis microbiology from European tobramycin trial in cystic fibrosis. J Cystic Fibrosis 2002: In press.

Hobson R, Gould I, Govan J. *Burkholderia (Pseudomonas) cepacia* as a cause of brain abscess secondary to chronic suppurative otitis media. Eur J Clin Microbiol Infect Dis 1995; 14:908-911.

Hutchinson ML, Govan JRW. Pathogenicity of microbes associated with cystic fibrosis. Microb and Infect 2000; 27:73-77.

Kenwood CJ, Livermore DM, James D, Warner M and the Pseudomonas Study Group. Antibmicrobial susceptibility of *Pseudomonas aeruginosa*: results of a UK survey and evaluation of the British Society for Antimicrobial Chemotherapy disc susceptibility test. J Antimicrob Chemother 2001; 47:789-799.

LiPuma JJ. *Burkholderia cepacia*: Management issues and new insights. Clin Chest Med 1998; 19:473-486.

Littlewood JM, Miller MG, Ghoneim AG, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet 1985; i: 865.

Livermore DM. β-lactamases in laboratory and clinical resistance. Clin Microbiol Revs 1995; 8:557-584.

Nikaido H. Prevention of drug access to bacterial targets: permeability barriers and active efflux. Science 1994; 264:382-388.

Nzula S, Vandamme P, Govan JRW. Influence of taxonomic status on the in *vitro* susceptibility of the *Burkholderia cepacia* complex. J Antimicrob Chemother 2002; 50:265-269.

Pitt TL, Kaufmann ME, Patel PS, Benge LCA, Gaskin S, Livermore DM. Type characterization and antibiotic susceptibility of *Burkholderia (Pseudomonas) cepacia* isolates from patients with cystic fibrosis in the United Kingdom and the Republic of Ireland. J Med Microbiol 1996; 44:203-210.

Ramsay BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Eng J Med 1999; 340:23-40.

Ratjen F, Doring G, Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. Lancet 2001; 358: 983-984.

Regelman WE, Elliott GR, Warwick WJ, Clawson CC. Reduction in sputum *Pseudomonas aeruginosa* density by antibiotics improves lung function in cystic fibrosis more than do bronchodilators and chest physiotherapy. Am Rev Resp Dis 1990; 141:914-921.

Saiman L. Antimicrobial resistance among Burkholderia, Stenotrophomonas and Alcaligenes studied by the CF Reference Center for susceptibility and synergy testing. Pediatr Pulmonol 1998; Suppl 17:118-119.

Seale TW, Thirkhill H, Tarpay M, Flux M, Rennert OM. Serotypes and antibiotic susceptibilities from single sputa of cystic fibrosis patients. J Clin Microbiol 1979; 9:72-78.

Thomassen MJ, Demko CA, Boxerbaum B, Stern RC, Kichenbrod PJ. Multiple isolates of *Pseudomonas aeruginosa* with differing antimicrobial susceptibility patterns from patients with cystic fibrosis. J Infect Dis 1979; 140:873-880.

Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. Lancet 1991; 338:725-726.

Wheat PF, Winstanley TG, Spencer RC. Effect of temperature on antimicrobial susceptibilities of *Pseudomonas aeruginosa*. J Clin Path 1985; 38:1055-1058.

Wolter JM, Kotsiou G, McCormack JG. Mixed morphotype testing of *Pseudomonas aeruginosa* cultures from cystic fibrosis patients. J Med Microbiol 1995; 42:220-224.

3. IDENTIFICATION OF INFECTION

3.1 Obtaining and interpreting specimens

Properly collected and processed specimens of respiratory secretions are essential in determining the appropriate use of antibiotics. Cough swabs are sensitive in detecting lower respiratory infection with *S. aureus* and *H. influenzae* but some cultures are positive where the infection is limited to the upper airways. Asymptomatic infections are not uncommon, particularly in relatively well patients who are not chronically infected with *P. aeruginosa*. Cough swabs are less sensitive and are also non-specific in detecting lower respiratory infection with *P. aeruginosa*. **However, it is reasonable to treat all patients from whom potential pathogens are isolated, and who are not already chronically infected, with appropriate antibiotics, whether they are symptomatic or not.**

3.2 Sputum

If the patient can produce sputum, a specimen should be obtained at each routine clinic visit and at the onset of an exacerbation of respiratory infection. In most cases, good sputum specimens reliably indicate lower respiratory infection. In patients who are minimally productive, it is useful to arrange for sputum pots to be available at home so that they can catch a specimen on the rare occasions when they do expectorate. Pseudomonas and Burkholderia species can be cultured from samples stored at room temperature for several days after collection; however, refrigeration is preferable and, ideally, samples should be processed within 2 or 3 hours to maximise the chances of isolating the full range of pathogens present.

When patients have difficulty producing a specimen, a physiotherapist may be successful in encouraging expectoration of a small sample from the patient.

Vomit sometimes contains copious amounts of swallowed sputum and is a potential source of respiratory secretions for culture.

Sputum production may be possible in non-productive, co-operative patients (generally aged over 5 years) by inhalation of hypertonic saline (4-6%). A specimen is usually obtained within a few minutes of inhalation (Carswell et al, 1995 [IIb]; O'Byrne & Inman, 1996 [IIb]; DeBoeck et al, 2000 [IIb]; Ball et al, 2001 [IIb]; Sagel et al, 2001 [IIb]). Bronchodilators given prophylactically may reduce the risk of transient bronchospasm as a result of the procedure.

3.3 Deep throat cough swab

A specimen should be obtained routinely at every clinic visit and at the onset of exacerbations of respiratory illness from patients who cannot expectorate. Children can be trained from the age of 2 years to cough when the swab is placed in the oropharynx. An experienced nurse or physiotherapist should collect these specimens, ideally after a physiotherapy session. Specimens are more likely to grow a pathogen if taken during the course of a viral respiratory infection. In one series of children with CF, throat swabs positive for *S. aureus* or *P. aeruginosa* were highly predictive of lower respiratory infection with these organisms but negative swabs may be associated with the presence of organisms in the lower respiratory tract (Ramsey et al, 1991 [III]). In another series in this age range, a negative throat culture was considered to be helpful in "ruling out" lower airway infection with *P. aeruginosa*; however, a positive culture did not reliably "rule in" the presence of *P. aeruginosa* in the lower respiratory tract (Rosenfeld et al, 1999 [III]).

3.4 Laryngeal aspirates

Laryngeal aspirates are obtained routinely at the Copenhagen CF Clinic from non-expectorating patients, and antibiotics are prescribed based on the results of monthly cultures. The specimens are obtained by passing a soft fine-bore suction catheter 8-10 cms into the nasopharynx. This stimulates coughing and suction is continued for a few seconds before the tube is removed. Saline is sucked through the tube into an attached collection chamber, which is sent for culture.

3.5 Bronchoalveolar lavage

The role of bronchoalveolar lavage is not yet firmly established. Experience suggests that bronchoscopy might usefully detect lower respiratory tract infection with *P. aeruginosa*, and more unusual pathogens, when there are worsening respiratory complications and negative culture results from the upper respiratory tract (Ramsey et al, 1991 [III]; Armstrong et al, 1996 [III]; Rosenfeld et al, 1999 [III]; Rosenfeld et al, 2001 [III]). In experienced hands it can be done as a day-case procedure with minimal risk although there is the slight possibility of spreading infection within the lungs (Connett et al, 1996 [III]; Ratjen et al, 2000 [III]).

3.6 Pseudomonas antibodies

The presence of Pseudomonas antibodies may suggest that the bacterium is present within the respiratory tract if the patient has cystic fibrosis (Pedersen et al, 1987 [III]; Elborn et al, 1993 [III]). There is good correlation between positive respiratory cultures and raised antibody levels to *P. aeruginosa* (Brett et al, 1986a [III]; Brett et al, 1986b [III]; Thanasekaraan et al, 1989 [III]; Pressler et al, 1990 [III]). On the other hand, a normal antibody level suggests there has been no tissue invasion by the *P. aeruginosa* and thus no immunological response. In these circumstances, if cultures are negative, it is very unlikely that *P. aeruginosa* is contributing to current respiratory problems.

Usually antibody levels are normal when the first positive *P. aeruginosa* culture occurs (Brett et al, 1987 [III]; Brett et al, 1992 [III]; Cordon et al, 1992 [III]). In such patients eradication with appropriate treatment is usually easily achieved. Regular monitoring of the Pseudomonas antibody levels, in part, compensates for the low sensitivity of airway cultures for *P. aeruginosa* in patients who do not produce much sputum. In patients with chronic *P. aeruginosa* infection the antibody level is invariably raised and the level correlates with the severity of the chest involvement (Brett et al, 1986a [III]). A rising antibody level indicates increasing tissue involvement and increasing immunological response. Such rises will prompt more intensive treatment and can be used to plan the long-term strategy e.g. frequency of courses of intravenous antibiotics (Pond et al, 1994 [III]). Successful long-term regular intravenous antibiotic regimens are associated with stable or even falling antibody levels. Certainly a rapidly rising level should encourage the clinician to start more aggressive antibiotic treatment.

It is helpful to measure Pseudomonas antibodies at each Annual Review (*Standards for the Clinical Management of Children and Adults with Cystic Fibrosis*. Cystic Fibrosis Trust, 2001 [IV]), at times of early *P. aeruginosa* infection (Brett et al, 1992 [III]; Elborn et al, 1993 [III]) and at the start of IV antibiotic treatment of pulmonary exacerbations in chronically infected patients.

Pseudomonas antibody tests can be arranged through either -
Dr. Ty Pitt, Laboratory of Hospital Infection, Central Public Health Laboratory,
61 Colindale Avenue, London NW9 5HT
or
Dr. Jimmy Gooi, Department of Immunology, St James's University Hospital,
Beckett Street, Leeds, LS9 7TF.

3.7 References

Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage and oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol 1996; 21:267-275.

Ball R, Conway SP, Brownlee KG, Morrison LJ. Value of nebulised hypertonic saline to induce sputum specimens in young children with cystic fibrosis. European Cystic Fibrosis Society Conference, Vienna, 2001. Poster 77.

Brett MM, Ghoneim ATM, Littlewood JM. Serum antibodies to *Pseudomonas aeruginosa* in cystic fibrosis. Arch Dis Child 1986a; 61:1114-1120

Brett MM, Ghoneim ATM, Littlewood JM, Losowsky MS. Development of enzyme linked immunosorbent assay (ELISA) to detect antibodies to *Pseudomonas aeruginosa* in the sera of patients with cystic fibrosis. J Clin Path 1986b; 39:1124-1129.

Brett MM, Ghoneim ATM, Littlewood JM. Serum IgG antibodies in patients with cystic fibrosis with early *Pseudomonas aeruginosa* infection. Arch Dis Child 1987; 62:357-361.

Brett MM, Simmonds EJ, Ghoneim ATM, Littlewood JM. The value of serum IgG titres against *Pseudomonas aeruginosa* in the management of early infection in cystic fibrosis. Arch Dis Child 1992; 67:1086-1088.

Carswell F, Raghuveer G, Silman C. Lung flora discovered by sputum induction in children with cystic fibrosis. Eur Resp Soc J 1995; 8 (Suppl 19): 575s

Connett GJ, Doull IJ, Keeping K, Warner JO. Flexible fibre-optic bronchoscopy in the management of lung complications in cystic fibrosis. Acta Paediatr 1996; 85:675-678.

Cordon SM, Elborn JS, Rayner RJ, Hiller EJ, Shale DJ. IgG antibodies in early *Pseudomonas aeruginosa* infection in cystic fibrosis. Arch Dis Child 1992; 67:737-740.

Cystic Fibrosis Trust. Standards for the Clinical Management of Children and Adults with Cystic Fibrosis. 2001.

De Boeck K, Alifier M, Vandeputte S. Sputum induction in young cystic fibrosis patients. Eur Respir J 2000; 16:91-94.

Elborn JS, Cordon SM, Shale DJ. Inflammatory response to first infection with *P. aeruginosa*. Pediatr Pulmonol 1993; 15:287-291.

O'Byrne PM, Inman MD. Induced sputum to assess airway inflammation in asthma. Eur Respir J 1996; 9:2435-2436.

Pedersen SS, Espersen F, Hoiby N. Diagnosis of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis by enzyme linked immunosorbent assay. J Clin Microbiol 1987; 25:1830-1836.

Pond M, Carr I, Littlewood JM, Conway SP. A longitudinal study of anti-pseudomonas ELISA in young adults with cystic fibrosis. 19th European Cystic Fibrosis Conference. Paris. 1994. Poster 24.

Pressler T, Pedersen SS, Espersen F, Hoiby N, Koch C. IgG subclass antibodies to *Pseudomonas aeruginosa* in sera from patients with chronic *Ps. aeruginosa* infection investigated by ELISA. Clin Exp Immunol 1990; 81:428-434.

Ramsey BW, Wentz KR, Smith AL, Richardson M, Williams-Warren J, Gibson R, et al. Predictive value of oropharyngeal cultures for identifying lower airway bacteria in cystic fibrosis patients. Am Rev Resp Dis 1991; 144:331-337.

Ratjen F, Rietschel E, Griese M, Ballmann M, Kleinau I, Doring G, et al. Fractional analysis of bronchoalveolar lavage fluid cytology in cystic fibrosis patients with normal lung function. Bronchoalveolar lavage for the evaluation of anti-inflammatory treatment (BEAT) study group. Eur Respir J 2000; 15:141-145.

Rosenfeld M, Emerson J, Accurso F, Armstrong D, Castile R, Grimwood K, et al. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. Pediatr Pulmonol 1999; 28:321-328.

Rosenfeld M, Gison RL, McNamara S, Emerson J, Burns JL, Castile R, et al. Early pulmonary infection, inflammation, and clinical outcomes in infants with cystic fibrosis. Pediatr Pulmonol 2001; 32:356-366.

Sagel SD, Kapsner R, Osberg I, Sontag MK, Accurso FJ. Airway inflammation in children with cystic fibrosis and healthy children assessed by sputum induction. Am J Respir Crit Care Med 2001; 164:1425-31.

Thanasekaraan V, Wiseman MS, Rayner RJ, Hiller EJ, Shale DJ. *Pseudomonas aeruginosa* antibodies in blood spots from patients with cystic fibrosis. Arch Dis Child 1989; 64:1599-1603.

4. ORAL ANTIBIOTICS IN CYSTIC FIBROSIS

It is particularly important, and possible, to either prevent, eradicate or control endobronchial infection by *S. aureus*, *H. influenzae* and *P. aeruginosa*, the common pathogens in cystic fibrosis (Elborn et al, 1996 [IV]). In the absence of appropriate antibiotic treatment, the abnormal respiratory secretions of the infant with CF soon become sequentially infected with *S. aureus* (Armstrong et al, 1996 [III]), *H. influenzae* and *P. aeruginosa* leading ultimately to death from progressive respiratory failure. Eradication of a particular organism is more easily achieved in the early stages soon after the culture becomes positive and 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.

4.1 Treatment of *Staphylococcus aureus* infection

Staphylococcus aureus is a significant pathogen in patients with cystic fibrosis. Positive respiratory cultures are associated with an immunological response suggesting the presence of tissue infection (Strandvik et al, 1990 [III]). Bronchoscopic cultures from untreated infants with CF identified by neonatal screening were positive for *S. aureus* in 31% of cases by 3 months of age although not all were symptomatic (Armstrong et al, 1996 [III]). Septicaemia (Aebischer et al, 2000 [IV]) and even fatal chest infections due solely to *S. aureus* occur in patients with cystic fibrosis. Thus, it is sensible to eradicate *S. aureus* from respiratory cultures even though the patient may appear well.

Aims. To prevent or eradicate *S. aureus* infection of the respiratory tract by the intermittent or long-term use of an anti-staphylococcal antibiotic (e.g. flucloxacillin) from the time of diagnosis.

Evidence. Infants with CF treated with a long-term anti-staphylococcal antibiotic (cloxacillin) had significantly fewer precipitins against *S. aureus* than had untreated infants (Lawson & Porter, 1976 [III]). Infants with CF identified by neonatal screening and treated with long-term flucloxacillin for the first 2 years had less frequent cough (evident at 6 months and significant by 18 months), less need for additional courses of antibiotic (3.7 versus 8.3 courses per year) and fewer positive respiratory cultures for *S. aureus* (17% versus 60%). Also they had fewer days in hospital during the second year (5 versus 19 days) and they were admitted for shorter periods (2.2 versus 6.4 days) (Weaver et al, 1994 [Ib]), although there was no difference in lung function (Beardsmore et al, 1995 [III]).

A US CF Foundation multicentre controlled trial of long-term cephalexin included 220 children less than 2 years old with mild chest involvement; 209 started but only 119 finished. 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* (25% of the cephalexin group versus 13% of controls) (Stutman et al, 2002 [Ib]). The authors concluded that long-term anti-staphylococcal treatment was not indicated. The trial was only published recently although the work was carried out in the early 1990s.

Others too have reported that prophylactic anti-staphylococcal treatment may increase the incidence of *P. aeruginosa*, as was the case in the first placebo-controlled trial of cephalexin therapy (Loening-Baucke et al, 1979 [Ib]). In Toronto, when prophylactic anti-staphylococcal therapy was given to all patients (1970-79), the median age of onset of *P. aeruginosa* infection was 3.4 years; but between 1980-89, when routine anti-staphylococcal treatment was abandoned, the mean age of onset of *P. aeruginosa* infection increased to 5.9 years (Parekh et al, 1998 [III]). Evidence from the German CF Registry also supports this finding (Ratjen et al, 2001a [III]). However, the increase in *P. aeruginosa* positive cultures is only of importance if early treatment of the organism, with a combination of a nebulised antibiotic and an oral or intravenous antibiotic, is not clinic policy

(Frederiksen et al, 1997 [IIb]). If there is no such policy of early anti-pseudomonal therapy – as is the case in some US and Canadian clinics (Stutman, 1996 [IV]; MacDonald et al, 1996 [IV]) – the possibility of causing an increased incidence of *P. aeruginosa* positive cultures is important because, if not treated, these will lead to an increased prevalence of chronic *P. aeruginosa* infection. Both long-term and intermittent flucloxacillin regimens would appear to be effective in preventing chronic staphylococcal infection.

In clinics where effective early intensive intermittent or prophylactic anti-staphylococcal treatment and early treatment of *P. aeruginosa* have been routine for some years, there is a very low prevalence of both chronic *S. aureus* and *P. aeruginosa* infection (Connolly et al, 1995 [III]; Frederiksen et al, 1997 [IIb]; Lee et al, 2001 [III]).

The prevalence of chronic *S. aureus* infection differs widely among Specialist CF Centres and Clinics, from less than 10%, where patients have been taking long-term flucloxacillin from diagnosis (Southern et al, 1993 [III]; Littlewood et al, 1995 [III]), to over 90% by 5-9 years in Milan, where no prophylaxis is prescribed (Padoan et al, 1996 [III]).

Long-term prophylactic flucloxacillin is effective in preventing or reducing the incidence of *S. aureus* infection and for the first 2 years of life reducing clinical symptoms and the need for additional antibiotics (Weaver et al, 1994 [Ib]). The ideal duration of such long-term treatment has not been determined; some clinics continue flucloxacillin indefinitely with no problems of toxicity or resistance (Southern et al, 1993 [III]); others stop the flucloxacillin at 2 to 3 years of age thereafter treating only when *S. aureus* is isolated from respiratory cultures (Szaff & Hoiby, 1981 [IV]). There is no published evidence that continuous anti-staphylococcal therapy is of benefit in children over the age of 2 years (Smyth & Walters, 2002 [Ia]).

Alternatives. An alternative approach to long-term flucloxacillin from diagnosis is a 2-week course of 2 appropriate antibiotics whenever *S. aureus* grows from respiratory cultures (Szaff & Hoiby, 1981 [IV]). A practical problem with this approach is the poor correlation of the results of upper respiratory tract cultures and those from bronchoalveolar lavage fluid (Ramsey al, 1991 [III]; Rosenfeld et al, 1999 [III]). However, it is unlikely that lower respiratory tract infections will go untreated if all positive throat swabs are treated. The regimen works well in Copenhagen, and chronic *S. aureus* infection is not a major problem there. However, all patients attend the clinic every month and treatment is early and vigorous. In the UK – where many patients still only have cultures performed every 2 or 3 months, or in the US, where some have even more infrequent cultures – it is likely that *S. aureus* infection will go unrecognised and untreated in some patients; the high prevalence of chronic *S. aureus* infection in many Specialist CF Centres and Clinics (>40%) suggests that this does occur.

There are no recent published comparisons between flucloxacillin and other anti-staphylococcal regimens e.g. erythromycin, cephalexin or azithromycin. These antibiotics should be as effective as flucloxacillin for prophylaxis although some *S. aureus* are resistant to the macrolides erythromycin and azithromycin and some to sodium fusidate. The acquisition of resistance to flucloxacillin (as in methicillin-resistant *Staphylococcus aureus* [MRSA]) is very rare in the context of CF and does not appear to develop as the result of its prolonged prophylactic use (Southern et al, 1993 [III]). However, MRSA now accounts for some 20-40% of hospital *S. aureus* in the UK.

Macrolides in cystic fibrosis. Long-term use of some macrolides such as erythromycin and azithromycin appears to have additional beneficial anti-inflammatory effects in patients with CF also infected with *P. aeruginosa* (Jaffe et al, 1998 [IV]; Wolter et al, 2002 [Ib]; Peckham, 2002 [IV]; Equi et al, 2002 [Ib]). 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 (Wolter et al, 2002 [Ib]). 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 FEV_1 <80%, showed significant benefit in those taking the azithromycin (Equi et al, 2002 [Ib]). Some clinicians are now using long-term azithromycin in patients chronically infected with *P. aeruginosa* when their progress is unsatisfactory.

Anti-staphylococcal therapy in CF has been the subject of a recent systematic review, which supported its efficacy (McCaffery et al, 1999 [Ia]; Elborn, 1999 [IV]).

Suggested regimen for prevention and treatment of *S. aureus*
- *All CF infants less than 2 years of age should receive long-term flucloxacillin from diagnosis [B].*

- *Some clinics will treat all patients with permanent flucloxacillin from diagnosis whatever their age. This should be the policy if there are problems with performing cultures every month or 6 weeks and at times of respiratory infections. If S. aureus does not grow on regular routine cultures after 2 years, an alternative regimen is to treat whenever a S. aureus positive culture is obtained, giving a 2-week course of anti-staphylococcal antibiotics [C].*

- *If S. aureus 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 2 weeks (sodium fusidate, azithromycin, erythromycin or clindamycin). Check cultures after 2 weeks treatment. If clear, continue long-term prophylactic flucloxacillin. Check if the S. aureus is MRSA, which would be resistant to flucloxacillin [C].*

- *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 S. aureus, give a course of 2 IV antibiotics (flucloxacillin or teicoplanin, with gentamicin or clindamycin) before accepting permanent infection. Bronchoscopy should be considered to exclude other organisms in the lower respiratory tract [C].*

- *If S. aureus 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].*

- *If a pathogen other than S. aureus grows from patients receiving long-term flucloxacillin, add a second appropriate antibiotic to cover the new pathogen but continue the flucloxacillin [C].*

4.2 Treatment of *Haemophilus influenzae* infection

The most common bacterial pathogen isolated from the respiratory cultures of young children with CF, who are already on long-term anti-staphylococcal prophylaxis, is *H. influenzae* (Littlewood, 1993 [III]; Connolly et al, 1995 [III]). The organism is a significant pathogen in CF particularly when present in high numbers (>10^6 CFU/g sputum) (Rayner et al, 1990 [III]) but the laboratory can overlook the organism unless special culture methods are used (Bilton et al, 1995 [IV]).

Aim. To treat and eradicate *H. influenzae* infection and prevent chronic infection.

Evidence. There are no trials to demonstrate benefit from eradication of *H. influenzae* from respiratory cultures in CF but the organism usually clears very quickly with appropriate therapy. It is a known respiratory pathogen and repeated growth over prolonged periods in some patients suggests that chronic infection can occur.

Suggested antibiotic use when *H. influenzae* is isolated

● *If <u>H. influenzae</u> 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 one week [C]. Suggested antibiotics include amoxycillin, co-amoxiclav, a second-generation cephalosporin or tetracycline (in adults only). Chloramphenicol is active but toxic. Most macrolides have poor activity but azithromycin is more potent (see Pharmacopoeia Sections 9.4 and 9.5).*

● *Cultures should be repeated after treatment, as negative cultures suggest clearance; repeat culture is essential if new symptoms persist [C]. If the cultures are still positive but the patient is well, note sensitivities and give further 2 - 4 weeks of an oral antibiotic, relying on weekly cultures to decide the length of treatments [C].*

● *If cultures are still positive after one month, the patient should have a 2-week course of IV antibiotics (see Section 6 and Pharmacopoeia Section 9.5) [C].*

● *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. Bronchoscopy with bronchoalveolar lavage may be helpful in children at this stage [C].*

● *If cultures remain positive despite intensive treatment or there are frequent recurrences of <u>H. influenzae</u> positive cultures after courses of treatment, a long-term anti-<u>H. influenzae</u> antibiotic should be considered, analogous to the use of anti-staphylococcal prophylaxis [C].*

4.3 An antibiotic active against *Haemophilus influenzae* at times of colds

The frequency of "colds" for which an additional antibiotic would be given has been recorded in one UK Specialist CF Centre as between 1 and 10 per year, with an average of 2.7 (3.7 for young children and 2.3 for those over 6 years) (Collinson et al, 1996 [III]). Interestingly infants with CF receiving long-term flucloxacillin also required an additional 3.7 courses of antibiotic each year (Weaver et al, 1994 [Ib]).

The difficulty in isolating the *H. influenzae* from CF sputum suggests that the organism is present in some patients even though routine cultures are negative (Bilton et al, 1995 [IV]). The report of additional bacterial infection in 20% of non-CF individuals who have viral upper respiratory infections and their accelerated recovery when antibiotics active against *H. influenzae* are used lends support to the practice (Kaiser et al, 1996 [IIb]).

Aim. To prevent additional *H. influenzae* infection at the time of viral respiratory infections.

Evidence. There are no trials in patients with CF to prove that giving an antibiotic active against *H. influenzae* at the time of presumed viral upper respiratory infections prevents secondary bacterial infection. However, there is a great deal of experience, both of clinicians, parents and patients supporting the practice.

Suggested practice with upper respiratory (presumed) viral infections

- *With all colds start an oral anti-<u>H. influenzae</u> antibiotic (e.g. amoxycillin) after sending a throat swab or sputum for culture; parents/patients should inform the Specialist CF Centre or Clinic they have started treatment and sent a 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 [B].*

- *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 even if the patient appears otherwise well [C].*

4.4 Treatment of early *Pseudomonas aeruginosa* infection

The success of early identification and treatment in preventing *Pseudomonas aeruginosa* infection becoming established and chronic frequently determines the patient's future quality of life and long-term survival.

There is increasing evidence that prevention of chronic *P. aeruginosa* infection has important beneficial effects for people who have cystic fibrosis. Those chronically infected with *P. aeruginosa* have more respiratory symptoms and significantly worse general health, a more rapid decline of their respiratory function (Kerem et al, 1990 [III]; Pamukcu et al, 1995 [III]), a more rapid deterioration in their chest X-ray scores (Kosorok et al, 2000 [IIb]) and significantly worse survival (Cystic Fibrosis Foundation, 1997 [IV]; Emerson et al, 2002 [III]). The age at onset of chronic *P. aeruginosa* infection is a predictor of age at death (Frederiksen et al, 1998 [IIb]).

Aim. To eradicate *P. aeruginosa* from the respiratory tract, thus avoiding the establishment of chronic infection.

Evidence. Nebulised colistin alone was observed to eradicate early *P. aeruginosa* infection in some patients (Littlewood et al, 1985 [IV]) as does nebulised tobramycin alone (Wiesemann et al, 1998 [Ib]; Ratjen et al, 2001b [III]).

When 3 weeks of nebulised colistin was used in combination with oral ciprofloxacin, eradication of *P. aeruginosa* was achieved in almost 80% of newly infected patients (Valerius et al, 1991 [Ib]; Frederiksen et al, 1997 [IIb]); a combination of inhaled tobramycin and colistin with oral ciprofloxacin was also effective (Vazquez et al, 1993 [IIb]).

A course of intravenous antibiotics alone was reported to eradicate *P. aeruginosa* in only 20 to 30% of patients (Steinkamp et al, 1989 [III]; Brett et al, 1992 [III]) but some of these patients were treated many months after the first positive cultures. Intravenous antibiotics are more effective than this if given very soon after the first isolation (Brett et al, 1992 [III]; Munck et al, 2001 [III]). Recent experience from the Copenhagen CF clinic suggests that the time before reappearance of a further *P. aeruginosa* positive culture can be increased from a median of 9 months to 18 months if the nebulised colistin and ciprofloxacin are given for 3 months after the appearance of the first positive culture (Frederiksen et al, 1997 [IIb]). With this treatment regimen, combined with patient segregation according to microbiological status, the probability of being free of chronic

P. aeruginosa infection 7 years after the first isolation increased to above 80% (Frederiksen et al, 1999 [III]).

Management after the first respiratory culture is reported positive for *P. aeruginosa*

● *Check the patient is not unwell and needing intravenous antibiotic treatment (see Section 6) [C].*

● *Repeat the respiratory culture [C].*

● *Check the Pseudomonas antibody level (see Section 3.6) [B].*

● *Start nebulised colistin and oral ciprofloxacin for 3 weeks; then repeat culture [A]. If the repeat culture is negative no further colistin or ciprofloxacin is given. However, some clinics advise continuing the colistin and ciprofloxacin for 3 months, which increases the median time to recurrence from 9 to 18 months [B].*

● *For asymptomatic children less than 3 years old and those older children who cannot swallow ciprofloxacin tablets, a liquid preparation of oral ciprofloxacin is available to give with the nebulised colistin. If the ciprofloxacin cannot be tolerated, nebulised colistin can be given alone in the first instance and may be successful in clearing the infection [C] as is inhaled tobramycin alone [A]. However, some clinicians recommend a 2-week course of intravenous antibiotics with the inhaled antibiotic if ciprofloxacin was not tolerated. If there are new symptoms or, if the culture does not clear in 3-4 weeks with nebulised colistin alone, continue the colistin and give a 2-week course of intravenous ceftazidime and tobramycin; then continue colistin for at least 3 months even if all cultures are negative for P. aeruginosa and the antibodies are normal [C].*

● *Ensure that regular cultures are performed at least monthly and particularly if there is a viral respiratory infection, when P. aeruginosa is more likely to be identified if present [B].*

Subsequent respiratory cultures positive for *P. aeruginosa*

● *Use the same regimen as for the first positive culture, but consider continuing nebulised colistin alone or with oral ciprofloxacin for 3 months [C].*

● *If there are further recurrences continue ciprofloxacin for 3 months and permanently give nebulised colistin. Also check patient's adherence to the nebulised colistin treatment, also the equipment and technique. Consider replacing the colistin with a nebulised preservative-free preparation of tobramycin (TOBI). Both genomic finger printing of the organisms and Pseudomonas antibody levels may be helpful in distinguishing between reinfection and failure of eradication [B].*

● *If P. aeruginosa fails to clear with oral ciprofloxacin and nebulised colistin, a course of 2 intravenous anti-pseudomonal antibiotics should be given. The nebulised antibiotic should be continued during the IV treatment [C].*

● *If P. aeruginosa persists after the intravenous and nebulised antibiotic treatment, a long-term nebulised anti-pseudomonal antibiotic (colistin) should be continued. Preservative-free tobramycin (TOBI) could be considered in those patients where treatment has recently failed to eradicate the organism and regular 3-monthly courses of intravenous antibiotics started [C].*

4.5 Courses of oral ciprofloxacin in patients chronically infected with *Pseudomonas aeruginosa* with increasing signs and symptoms or colds

In patients chronically infected with *P. aeruginosa* it is common practice to prescribe a 2-week course of ciprofloxacin, rather than an anti-*H. influenzae* drug, for colds or mild exacerbations so as to prevent more serious exacerbations and avoid the need for intravenous treatment.

Aim. To treat respiratory exacerbations in patients chronically infected with *P. aeruginosa*, which is sensitive to the drug and return them to a stable state.

Evidence. There is some evidence that such patients improve more rapidly than expected by chance after starting oral ciprofloxacin – however, regular courses of ciprofloxacin have shown little benefit in chronically infected adults (Sheldon et al, 1993 [Ib]).

Suggested use of oral ciprofloxacin with colds and early exacerbations
- *A 2 week course of ciprofloxacin should 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 [A].*

- *These patients will usually be taking a regular nebulised anti-pseudomonal antibiotic, which should be continued [C].*

4.6 References

Aebischer CC, Aebi C, Schoni MH. *Staphylococcus aureus* septicaemia in a patient with cystic fibrosis. Eur J Pediatr 2000; 159:689–691.

Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage and oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. Pediatr Pulmonol 1996; 21:267-275.

Beardsmore CS. Lung function from infancy to school age in cystic fibrosis. Arch Dis Child 1995; 73:519-523.

Bilton D, Pye A, Johnson MM, Mitchell JL, Dodd M, Webb AK, et al. The isolation and characterization of non-typeable *Haemophilus influenzae* from the sputum of adult cystic fibrosis patients. Eur Respir J 1995; 8:948-953.

Brett MM, Simmonds EJ, Ghoneim ATM, Littlewood JM. The use of serum IgG titres against *Pseudomonas aeruginosa* in the management of early Pseudomonal infection in cystic fibrosis. Arch Dis Child 1992; 67:1086-1088.

Collinson J, Nicholson KG, Cancio E, Ashman J, Ireland DC, Hammersley V, et al. Effects of upper respiratory tract infections in patients with cystic fibrosis. Thorax 1996; 51:1115-1122.

Connolly SA, Littlewood JM, Littlewood AE, Denton M. Present day condition and management of children attending a specialist CF centre. I Respiratory. 20th European Cystic Fibrosis Congress, Brussels, 1995. Poster 62.

Cystic Fibrosis Foundation, Patient Registry 1996 Annual Data Report, Bethesda, Maryland, 1997.

Elborn S, Dodge J, Littlewood J. Cystic Fibrosis Pulmonary Infections: The UK Experience. In: Bauernfeind A, Marks M I, Strandvik B, editors. Cystic Fibrosis Pulmonary Infections: Lessons from Around the World. Basel Boston Berlin: Birkhauser Verlag, 1996:303-314.

Elborn JS. Treatment of *Staphylococcus aureus* in cystic fibrosis. Thorax 1999; 54:377-379.

Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol 2002; 34:91-100.

Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised placebo controlled crossover trial. Lancet 2002; 360:978-984.

Frederiksen B, Koch C, Hoiby N. Antibiotic treatment at time of initial colonisation with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration in pulmonary function in patients with cystic fibrosis. Pediatr Pulmonol 1997; 23:330-335.

Frederiksen B, Hoiby N, Koch C. Age at onset of chronic pulmonary *Pseudomonas aeruginosa* infection is a predictor for survival in cystic fibrosis. Pediatr Pulmonol 1998; Suppl 17:325. Poster 432.

Frederiksen B, Koch C, Hoiby N. Changing epidemiology of *Pseudomonas aeruginosa* infection in Danish cystic fibrosis patients (1974-1995). Pediatr Pulmonol 1999; 28:159-166.

Jaffe A, Francis J, Rosenthal M, Bush A. Long-term azithromycin may improve lung function in children with cystic fibrosis. Lancet 1998; 351:420.

Kaiser L, Lew D, Hirschel B, Auckenthaler R, Morabia A, Heald A, et al. Effects of antibiotic treatment in the subset of common-cold patients who have bacteria in nasopharygeal secretions. Lancet 1996; 347:1507-1510.

Kerem E, Corey M, Gold R, Levison H. pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonisation with *Pseudomonas aeruginosa*. J Pediatr 1990; 116:714-719.

Kosorok MR, Zeng L, West SE, Rock MJ, Splaingard M, Laxova A, et al. Acceleration of lung disease after *Pseudomonas aeruginosa* acquisition. Pediatr Pulmonol 2000; Suppl 20:313.

Lawson D, Porter J. Serum precipitins against respiratory pathogens in 522 'normal' children, and 48 cases of cystic fibrosis treated with cloxacillin. Arch Dis Child 1976; 51:890-891.

Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Reduction in the prevalence of *Pseudomonas aeruginosa* infection by modern management. Pediatr Pulmonol 2001; Suppl 22:294. Poster 397.

Littlewood JM, Miller MG, Ghoneim AT, Ramsden CH. Nebulised colomycin for early Pseudomonas colonisation in cystic fibrosis. Lancet 1985;i: 865.

Littlewood JM. Value of comprehensive assessment and investigation in the management of cystic fibrosis. In: Escobar H, Basquero L, Suarez L, editors. Clinical Ecology of Cystic Fibrosis. Amsterdam: Elsevier, 1993:181-187.

Littlewood JM, Littlewood AE, McLaughlin S, Shapiro L, Connolly S. 20 years continuous neonatal screening in one hospital; progress of the 37 patients and their families. Pediatr Pulmonol 1995; Suppl 12:284.

Loening-Baucke VA, Mischler E, Myers MG. A placebo-controlled trial of cephalexin therapy in ambulatory management of patients with cystic fibrosis. J Pediatr 1979; 95:630-637.

MacDonald N, Corey M, Morrison R. The General Approach to Cystic Fibrosis Pulmonary Infection in Canada. In: Bauernfeind A, Marks MI, Strandvik B. Cystic Fibrosis Pulmonary Infections. Lessons from Around the World. Basel, Boston Berlin: Birkhauser Verlag 1996:111-118.

McCaffery K, Olver RE, Franklin M, Mukhopadhyay S. Systematic review of anti-staphylococcal therapy in cystic fibrosis. Thorax 1999; 54:380-383.

Munck A, Bonacorsi S, Mariani-Kurkdjian P, Lebourgeois M, Geradin M, Brahimi N, et al. Genotypic characterisation of *Pseudomonas aeruginosa* strains recovered from patients with cystic fibrosis after initial and subsequent colonization. Pediatr Pulmonol 2001; 32:288-292.

Pamukcu A, Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonisation on lung function and anthropometric variables in children with cystic fibrosis. Pediatr Pulmonol 1995; 19:10-15.

Parekh N, Subbarao P, Sweezey N, Matlow A, Corey M. Association between prophylactic antibiotic usage and early onset of *Pseudomonas aeruginosa*. Pediatr Pulmonol 1998; Suppl 17:324. Poster 426.

Peckham DG. Macrolide antibiotics and cystic fibrosis. Thorax 2002; 57:189-190.

Podoan R, Pianaroli A, Giunta A. The general approach to cystic fibrosis pulmonary infection in Italy. In: Bauernfeind A, Marks MI, Strandvik B, editors. Cystic Fibrosis Pulmonary Infections: Lessons from Around the World. Basel, Boston, Berlin: Birkhauser Verlag, 1996:209-222.

Ratjen F, Comes G, Paul K, Posselt HG, Wagner TO, Harms K. Effect of continuous antistaphylococcal therapy on the rate of *P. aeruginosa* acquisition in patients with cystic fibrosis. Pediatr Pulmonol 2001a; 31:13-16.

Ratjen F. Doring G. Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. Lancet 2001b; 358:983-4.

Ramsey BW, Wentz KR, Smith AL, Richardson M, Williams-Warren J, Hedges DL, et al. Predictive value of oropharyngeal cultures for identifying lower airway bacteria in cystic fibrosis patients. Am Rev Respir Dis 1991; 144:331-337.

Rosenfeld M, Emerson J, Accurso F, Armstrong D, Castile R, Grimwood K, et al. Diagnostic accuracy of oropharyngeal cultures in infants and young children with cystic fibrosis. Pediatr Pulmonol 1999; 28:321-8.

Rayner RJ, Hiller EJ, Ispahani P, Baker M. Haemophilus infection in cystic fibrosis. Arch Dis Child 1990; 65:255-258.

Smyth A, Walters S. Prophylactic antibiotics for cystic fibrosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Southern KW, Littlewood AE, Littlewood JM. The prevalence and significance of chronic *Staphylococcus aureus* infection in patients with cystic fibrosis on long-term flucloxacillin. In: Escobar H, Baquero CF, Svarez L, editors. Clinical Ecology of Cystic Fibrosis. Amsterdam, Elsevier Science Publishers, 1993; 129-130.

Steinkamp G, Tummler B, Malottke R, Von der Hardt A. Treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis. Arch Dis Child 1989; 64:1022-1028.

Sheldon CD, Assoufi BK, Hodson ME. Regular three monthly oral ciprofloxacin in adult cystic fibrosis patients infected with *Pseudomonas aeruginosa*. Respir Med 1993; 87:587-593.

Southern KW, Littlewood AE, Littlewood JM. The prevalence and significance of chronic *Staphylococcus aureus* infection in patients with cystic fibrosis on long-term flucloxacillin. In: Escobar H, Baquero CF, Svarez L, editors. Clinical Ecology of Cystic Fibrosis. Amsterdam: Elsevier Science Publishers, 1993: 129-130.

Strandvik B, Hollsing A, Mollby R, Granstrom M. Anti-staphylococcal antibodies in cystic fibrosis. Infection 1990; 18:170-172.

Stutman HR. The general approach to cystic fibrosis-related pulmonary infection in the United States. In: Bauernfeind A, Marks MI, Strandvik B, editors. Cystic Fibrosis Pulmonary Infections: Lessons from Around the World. Basel, Boston Berlin: Birkhauser Verlag 1996: 99-110.

Stutman HR, Lieberman JM, Nussbaum E, Marks MI. Antibiotic prophylaxis in infants and young children with cystic fibrosis: a randomized controlled trial. J Pediatr 2002; 140:299-305.

Szaff M, Hoiby N. Antibiotic treatment of *Staphylococcus aureus* infection in cystic fibrosis. Monogr Paediatr 1981; 14:108-114.

Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* infection in cystic fibrosis by early treatment. Lancet 1991; 338:725-726.

Vazquez C, Municio M, Corera M, Gaztelurrutia L, Sojo A, Vitoria JC. Early treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis. Acta Paediatr 1993; 82:308-309.

Weaver LT, Green MG, Nicholson K, Mills J, Heeley ME, Kuzemko JA, et al. Prognosis in cystic fibrosis treated with continuous flucloxacillin from the neonatal period. Arch Dis Child 1994; 70:84-89.

Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G. Placebo-controlled double blind randomized study of aerosolized tobramycin for early treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis. Pediatr Pulmonol 1998; 25:88-92.

Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. Thorax 2002; 57:121-216.

5. NEBULISED ANTIBIOTICS

5.1 Introduction

During childhood and adolescence the majority of patients with cystic fibrosis become first colonised, then chronically infected, with *P. aeruginosa*. Acquisition of this organism is associated with a worse prognosis (Wilmott et al, 1985 [III]; Kerem et al, 1990 [III]; Pamukcu et al, 1995 [III]; Cystic Fibrosis Foundation, 1997 [IV]; Frederiksen et al, 1997 [IIb]; Kosorok et al, 2000 [III]; Emerson et al, 2002 [III]).

Regular courses of intravenous antibiotics have improved survival by reducing sputum load and maintaining pulmonary function but they interfere with the activities of daily living. The prescription of nebulised antibiotics for home use by patients with CF is increasing. However, experienced physicians working in Specialist CF Centres have shown considerable variability in their prescribing practices for nebulised antibiotics (Taylor & Hodson, 1993 [IV]; Littlewood et al, 1993 [IV]) despite the fact that published evidence supports their effectiveness (Mukhopadhyay et al, 1996 [Ia]; Ryan et al, 2002 [Ia]).

5.2 Clinical Indications
5.2.1 Delay or prevention of chronic infection with *Pseudomonas aeruginosa*

Evidence. Chronic infection is defined as the regular culture of *P. aeruginosa* from the sputum or respiratory secretions, on 2 or more occasions extending over 6 months or a shorter period if accompanied by a sustained rise in anti-Pseudomonas antibodies (Brett et al, 1992 [III]; *Pseudomonas aeruginosa Infection in People with Cystic Fibrosis.* Cystic Fibrosis Trust, 2001 [IV]). The introduction of nebulised colistin or tobramycin at the time of initial colonisation with *P. aeruginosa* may reduce and delay chronic colonisation (Littlewood et al, 1985 [IV]; Valerius et al, 1991 [Ib]; Wiesemann et al, 1998 [Ib]; Ratjen et al, 2001 [III]). In an uncontrolled trial, where nebulised colistin was given to 7 children with CF at time of first isolation of *P. aeruginosa*, the frequency of positive cultures for *P. aeruginosa* was reduced from 46% to 6% (Littlewood et al, 1985 [IV]). In a controlled prospective study, a combination of colistin and oral ciprofloxacin initiated at time of initial colonisation with *P. aeruginosa*, prevented or delayed chronic infection for 18 months (Valerius et al, 1991 [Ib]). A further study by the same group has confirmed their findings and suggested that persistent infection with *P. aeruginosa* could be delayed for even longer (Frederiksen et al, 1997 [IIb]). When 80 mg tobramycin was inhaled twice-daily for 12 months, *P. aeruginosa* was eradicated from 14 of 15 patients and Pseudomonas antibody levels reduced to zero (Ratjen et al, 2001 [III]).

These results suggest a definitive role for the introduction of nebulised antibiotics when *P. aeruginosa* is first isolated from sputum or throat swab.

Prophylactic use of inhaled gentamicin is reported to delay the acquisition of *P. aeruginosa* infection and decrease disease progression in children with cystic fibrosis. Between 1986 and 1999 all 28 patients with CF at risk of acquiring *P. aeruginosa* infection received inhaled gentamicin for a minimum of 3 years (80 mg bd for those <12 months; 120 mg for those >12 months). None of the 12 patients who continued the treatment throughout the whole study period developed *P. aeruginosa* infection but 7 of the 16 patients who discontinued the treatment for one reason or another developed chronic *P. aeruginosa* infection (Heinzi et al, 2002 [IV]).

Recommendation
- *See Section 4.4 for treatment of early P. aeruginosa.*

5.2.2 Prevention of clinical deterioration in patients chronically infected with *Pseudomonas aeruginosa*

Evidence. Regular nebulised antibiotics have been used to reduce the rate of deterioration of respiratory function in patients chronically infected with *P. aeruginosa*. An early controlled trial compared twice-daily nebulised 80 mg of gentamicin and 1 gm of carbenicillin against placebo (Hodson et al, 1981 [IIb]). In the study group that received the active drugs for 6 months, there was a reduction in hospital admissions for infective exacerbations and pulmonary function was maintained. Nebulised treatment was cost-effective because of the reduced hospital costs.

A double blind placebo controlled study of twice-daily inhalations of 1 million units of colistin in patients chronically infected with *P. aeruginosa* showed the treatment was superior to the placebo in terms of significantly better symptom scores, maintenance of respiratory function and inflammatory parameters (Jensen et al, 1987 [Ib]).

In a recent randomised crossover study 71 patients with CF received 1 month of placebo and 1 month of high dose nebulised tobramycin (600 mg/day) (Ramsay et al, 1993 [Ib]). The high dose of tobramycin was used to increase the bactericidal dose of antibiotic in the sputum against tobramycin-sensitive *P. aeruginosa*. There was a significant improvement in pulmonary function and a reduction of *P. aeruginosa* in the sputum. Bacterial resistance patterns were similar during the active and placebo part of the drug study. No ototoxicity or nephrotoxicity was observed.

These results suggest high-dose nebulised tobramycin is clinically effective, safe and does not rapidly promote bacterial resistance.

The same group undertook a large phase III trial including 520 patients, of whom 464 completed the trial. The patients took 300 mg of preservative-free, non-pyrogenic sterile tobramycin (TOBI) twice-daily during alternate months. The treated patients had improved pulmonary function, decreased sputum *P. aeruginosa* density, reduced hospitalisations and reduced use of other anti-pseudomonal antibiotics. Treatment with the preservative free tobramycin 300 mg twice-daily was associated with increased tobramycin mean inhibitory concentrations (MICs) at the end of the study in 15% of the treated, compared with 3% of the placebo patients (Ramsay et al, 1999 [Ib]; Burns et al 1999 [III]). Adolescent patients appeared to respond particularly well and after 92 weeks of the alternate month therapy with preservative free tobramycin the treated patients showed FEV_1 improvements of 14.3% compared with 1.8% for controls (Moss, 2002 [Ib]).

In the UK, in a comparative study of 1 month's twice-daily nebulised 300 mg of preservative free tobramycin (TOBI) and 1 mega unit of nebulised colistin sulphomethate sodium (Colomycin) both treatments reduced the bacterial content of the sputum significantly and increased the FEV_1 of the two groups by 6.7% and 0.37% respectively (Hodson et al, 2002 [IIb]; Govan, 2002 [IIb]). At present colistin sulphomethate sodium (Colomycin) and preservative free tobramycin (TOBI) are the only 2 antibiotics licensed in the UK for nebulisation in people with cystic fibrosis.

A meta-analysis review of five randomised controlled trials (Mukhopadhyay et al, 1996 [Ia]) and a Cochrane review (Ryan et al, 2002 [Ia]) confirmed the benefit for nebulised anti-pseudomonal antibiotic therapy for patients with CF who have chronic *P. aeruginosa* infection and there were no demonstrable serious adverse effects.

Although there is no evidence to suggest that nebulised antibiotics used as an adjunct to a course of intravenous antibiotics augment clinical improvement in chronically infected patients (Stephens et al, 1983 [IIb]), intravenous tobramycin and ticarcillin plus inhaled tobramycin resulted in temporary eradication of *P. aeruginosa* in 63% of patients compared to 25% in the intravenous

only group. Also the addition of nebulised amikacin to a regimen of intravenous amikacin and ceftazidime transiently eradicated *P. aeruginosa* from the sputum (as evidenced by negative cultures) in 70% of patients and in 41% of those receiving only intravenous therapy (Schaad et al, 1987 [Ib]).

Nebulised antibiotics are not a suitable alternative to intravenous antibiotics for infective exacerbations.

Recommendations for patients chronically infected with *Pseudomonas aeruginosa*
- *All patients who are chronically infected with P. aeruginosa should be considered for regular nebulised anti-pseudomonal antibiotic treatment [A].*

- *Initially colistin should be given [B].*

- *If colistin is not tolerated or clinical progress is unsatisfactory, preservative free tobramycin (TOBI) should be used [C]. Although the standard intravenous tobramycin preparation, and also intravenous gentamicin, have been widely used for inhalation by people with CF in the UK for over 20 years without major problems, neither preparation is licensed for inhalation and it is advisable to use the preservative free preparation of tobramycin (TOBI), which is licensed for inhalation in cystic fibrosis. Phenol-free tobramycin is available for IV use and is the recommended preparation if it is decided to prescribe tobramycin for inhalation other than in the form of TOBI [C].*

5.3 Assessment and administration

Patients should be carefully assessed before treatment with nebulised antibiotics. Hypertonic solutions may cause bronchospasm and the severity is usually related to the hypertonicity of the solution. Bronchodilators should be given before the antibiotic (Dodd et al, 1997 [III]); bronchoconstriction usually occurs immediately after the administration of the antibiotic (Madison et al, 1994 [III]). A mouthpiece is preferable to a mask to maximise pulmonary deposition (Everard et al, 1993 [III]) although small children below 3 years will usually require a mask held firmly on the face (Everard et al, 1992 [III]). Relaxed tidal breathing through the mouth, not the nose, is ideal (Newman et al, 1988 [III]).

Recommendations
- *A recent sputum culture should be used to determine which antibiotic to prescribe, with the choice based on the observed susceptibility patterns [A].*

- *Each patient should be given a hospital-supervised dose after chest physiotherapy [B].*

- *Spirometry should be performed before and immediately after the administration of the test dose of nebulised antibiotic. Small children should be observed for audible wheeze, cough or distress and the chest checked for bronchospasm with a stethoscope [B].*

- *Antibiotic solutions used for nebulisation should not be hypertonic and a bronchodilator should precede the nebulised antibiotic. Maximal bronchoconstriction to nebulised antibiotics usually occurs immediately after administration. Bronchoconstriction is usually related to hypertonicity of the solution [B].*

- *Nebulised antibiotics should be taken after physiotherapy and bronchodilators to ensure maximum deposition and protection from bronchoconstriction [B].*

- *A mouthpiece is preferable to a facemask to maximise pulmonary deposition [B]. Small children below 3 years old and babies will usually require a mask held firmly on the face [C].*

- *Relaxed tidal volume breathing through the mouth and not the nose is ideal [B]. A nose clip will increase the efficiency of delivery to the lungs in some patients but is not popular in practice and is not used by the majority [B].*

- *Adherence to treatment should be checked after a period of home use. Irregular usage is not recommended and is a reason for stopping treatment [C].*

5.4 Distribution of nebulised antibiotic in the lung

Overall, about 10% of a nebulised drug is delivered to the lungs. A study in volunteers and 5 mechanically ventilated patients who received 300 mg of nebulised tobramycin found 5.5% of the initial dose was excreted in the urine of both groups. A piece of normal lung removed at thoracotomy showed mean lung tissue tobramycin concentrations of 5.5 ug/g and 3.61 ug/g of lung tissue at 4 and 12 hours (Le Conte et al, 1993 [III]).

Systemic absorption of nebulised aminoglycosides does occur in patients but the amount absorbed is small at 0.5% of the dose given (Smith et al, 1989 [III]).

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 (Geers et al, 1987 [IIb]).

5.5 Antibiotic choice and formulation

The polymyxin antibiotic colistin (Colomycin) and the aminoglycosides tobramycin and gentamicin are the most commonly prescribed nebulised antibiotics in the UK. Colistin (Colomycin) and the preservative-free preparation of tobramycin (TOBI) are currently the only antibiotics licensed in the UK for inhalation. Tobramycin has greater activity than gentamicin against *P. aeruginosa*. Colistin has excellent anti-pseudomonal activity and although resistance has been reported it is very rare and is usually less of a problem than with aminoglycosides (Govan, 2002 [IIb]). *Burkholderia cepacia* is always resistant to colistin.

Recommendations
- *Colistin is the drug of first choice for nebulised use [C].*

- *Tobramycin is preferable to gentamicin for chronic <u>Pseudomonas aeruginosa</u> infection [B]. Preservative free tobramycin should be used and the licensed preparation (TOBI) should be used where possible. Phenol-free tobramycin is available for IV use and is the recommended preparation if it is decided to prescribe tobramycin for inhalation other than in the form of TOBI [C].*

- *Nebulised antibiotics are prescribed twice a day for home use [B].*

5.6 Antibiotic safety

Resistance
Concern has been expressed that bacterial resistance will develop with the administration of sublethal twice-daily doses of aerosolised antibiotics. Bacterial resistance does occur but is often

intermittent and adaptive and not related to clinical deterioration (Hodson et al, 1981 [Ib]; Barclay et al, 1996 [III]). There is no confirmatory evidence that the use of nebulised antibiotics in the presence of resistant bacteria leads to increased colonisation of the bronchial tree with these resistant organisms. *Burkholderia cepacia* is always resistant to colistin, which should not be used if the species is the sole sputum pathogen. There is no published literature on the use of nebulised antibiotics for *Burkholderia cepacia*. A recent randomised double blind controlled trial of nebulised taurolidine (4 ml of 2% solution twice-daily) in adults with cystic fibrosis reduced sputum volume and viscosity but did not alter *B. cepacia* counts or improve spirometry (Ledson et al, 1998 [Ib]).

Recommendation
● *Colistin should not be used if* <u>*B. cepacia*</u> *is the sole pathogen in the sputum [C].*

Environmental safety
Concern has been expressed that the liberal use of nebulised antibiotics may be a health hazard to medical personnel and constitute a threat to the hospital and home environment. Occasionally members of staff caring for patients using nebulised antibiotics have experienced cutaneous rashes and bronchoconstriction. It has been suggested that polluting the hospital atmosphere may lead to the establishment of resistant organisms particularly on intensive care units. There is no published evidence to support this concern. Patients often stop their nebulised antibiotics when they are receiving intravenous antibiotics although these should be continued if an attempt is being made to eradicate a recent early *P. aeruginosa* infection e.g. when oral ciprofloxacin and nebulised colistin have failed. At home, patients should nebulise their antibiotics in a separate room. They do not need to vent their exhaled antibiotics for safety reasons, although they may wish to do so to eliminate the odour.

Recommendations
● *In hospital, a nebuliser should be fitted with a high efficiency breathing filter on the expiratory port, to prevent environmental contamination [C].*

● *It is advisable for patients to receive nebulised antibiotics in a separate area from other patients [C].*

● *If the patient has a sibling with cystic fibrosis the use of a filter is mandatory [C].*

● *Mothers with CF who have young children should use a filter when nebulising antibiotics [C].*

Patient Safety
The respiratory side effects of aerosolised antibiotics are mainly limited to bronchoconstriction at time of delivery. Cutaneous rashes are rare but may occur with nebulised drugs. A sore mouth may be due to *Candida albicans* infection although the incidence is not known.

During pregnancy intravenous aminoglycosides cross the placenta. In people with CF repeated courses of high dose intravenous aminoglycosides have been associated with deafness and renal damage (McRorie et al, 1989 [IV]) but these side effects have not been reported with nebulised therapy.

Recommendations
● *If a facemask is used the face should be washed after nebulisation [C].*

● *Nebulised antibiotics should be prescribed with caution during pregnancy but, on the available evidence, they are not contra-indicated [C].*

Nebulisers may act as a source of bacterial contamination (Pitchford et al, 1987 [IV]; Hutchinson et al, 1996 [III]). Nosocomial acquisition of *B. cepacia* has been associated with the use of humidifiers and nebulisers (Burdge et al, 1993 [III]). Respiratory equipment has been implicated as the source of spread of *B. cepacia* in immunosuppressed patients (Yamagishi et al, 1993 [III]). Incorrect care of a nebuliser/compressor system may result in an inefficient system for drug delivery and a potential hazard to the patient and environment.

Recommendations

- *Patients should clean and thoroughly dry their nebulisers after every use. Some types of nebuliser can be placed in a dishwasher [B].*

- *Patients infected with <u>B. cepacia</u> who are taking other nebulised drugs should have their own compressors and these should not be used subsequently by other patients [B].*

- *An electrical compressor should have an inlet filter, which should be changed every 3 months [C].*

- *There should also be a bacterial filter in line to prevent the patient receiving contaminants from the compressor. These filters should be changed annually or between patients [C].*

- *Hospitals issuing nebuliser/compressor systems should arrange for their regular servicing. Patients who have been required to purchase their own nebuliser compressor systems should have their equipment serviced by the hospital where they attend for their CF care [C].*

5.7 Antibiotic delivery

Antibiotics are available as solutions or powder. They are reconstituted as a solution using saline or water as a diluent to a volume of 4 ml (2.5 ml for a low residual volume nebuliser).

Nebulisation should take no longer then 10 minutes in order to ensure maximum compliance. The requirements of a system for aerosolising antibiotics may differ from those required for other solutions.

Recommendations

- *To prepare isotonic solutions of colistin suitable for nebulisation [B]*
  2 megaunits in 4.0 ml -> add 2 ml water + 2 ml of normal saline
  2 megaunits in 2.5 ml -> add 1.5 ml water +1 ml normal saline
  2 megaunits in 3.0 ml -> add 2 mls water +1 ml normal saline
  For children the following are suitable
  1 megaunit + 1 ml water + 1 ml saline
  1 megaunit + 1 ml water + 2 ml saline

- *Details of drugs and dosages are presented in Section 9. For adults: colistin 2 megaunits twice-daily. For preservative tobramycin (TOBI) 300mg twice-daily on alternate months for all patients over 6 years of age [A]. If the phenol-free IV preparation of tobramycin is used a suitable dose is 80-160 mg twice-daily. [C].*

5.8 Recommended nebuliser-compressor systems for antibiotics

The following are recommended
- *Use an active venturi nebuliser (breath assisted) e.g. Ventstream or Pari LC Plus 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 [B].*

- *Patients provided with high flow compressors (more than 8 litres per minute) should use an active venturi nebuliser [B].*

- *The Pari LC Plus is recommended for the administration of preservative free tobramycin (TOBI) [A].*

Continuous innovative improvements are taking place to meet patient requirements; one such is the Adaptive Aerosol Delivery System (AAD) (Profile Respiratory Systems [Medic-Aid Ltd]), Heath Place, Bognor Regis, West Sussex PO22 9SL) which targets antibiotic delivery to the first part of the respiratory cycle. A recent multicentre trial compared the use of the AAD and conventional high output nebuliser system in 259 patients with cystic fibrosis. 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 (Marsden et al, 2002 [Ib]; Dodd et al, 2002 [Ib]; Conway et al, 2002 [Ib]). The use of bronchodilator solution in patients using AAD with colistin had a positive effect on maintaining both short and long-term FEV_1, as opposed to bronchodilator via a metered dose inhaler or dry powder inhaler (Dodd et al, 2002 [Ib]). In another study, using the AAD system, colistin in doses up to 2 mega units dissolved in 2 ml of normal saline was well tolerated (Adeboyeku et al, 2001 [Ib]).

5.9 References

Adeboyeku DU, Agent P, Jackson V, Hodson M. A double blind randomised study to compare the safety and tolerance of differing concentrations of nebulised colistin administered using the Halolite in cystic fibrosis patients. Pediatr Pulmonol 2001; Suppl 22:288. Poster 339.

Barclay ML, Begg EJ, Chambers ST, Thornley PE, Pattemore PK, Grimwood K. Adaptive resistance to tobramycin in *Pseudomonas aeruginosa* lung infection in cystic fibrosis. J Antimicrob Chemother 1996; 37:1155-1164.

Brett MM, Simmonds EJ, Ghoneim ATM, Littlewood JM. The use of serum IgG titres against *Pseudomonas aeruginosa* in the management of early Pseudomonal infection in cystic fibrosis. Arch Dis Child 1992; 67:1086-1088.

Burdge DR, Nakiena EM, Noble MA. Case-control and vector studies of nosocomial acquisition of *Pseudomonas cepacia* in adult patients with cystic fibrosis. Infect Control Hosp Epidemiol 1993; 14:127-130.

Burns JL, Van Dalfsen JM, Shawar RM, Otto KL, Garber RL, Quan JM et al. Effect of chronic intermittent administration of inhaled tobramycin on respiratory microbiological flora in patients with cystic fibrosis. J Infect Dis 1999; 179:1190-1196.

Conway SP, Dodd ME, Marsden RJ, Paul EA, Weller PH. Comparison of compliance in cystic fibrosis patients using either a Halolite Adaptive Aerosol Delivery (AAD) system or a conventional high output nebulizer system. European Cystic Fibrosis Society Meeting Genoa, 2002.

Cystic Fibrosis Foundation Patient Registry 1996 Annual Data Report, Bethesda, Maryland, August 1997.

Cystic Fibrosis Trust's Infection Control Group. *Pseudomonas aeruginosa* infection in people with cystic fibrosis. Suggestions for prevention and control. 2001.

Dodd ME, Abbott J, Maddison J, Moorcroft AJ, Webb AK. The effect of the tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis. Thorax 1997; 52:656-658.

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.

Emerson J, Rosenfeld M, McNamara S, Ramsay B, Gibson RL. *Pseudomonas aeruginosa* and other predictors of mortality and morbidity in young children with cystic fibrosis. Pediatr Pulmonol 2002; 34:91-100.

Everard M, Clark GR, Milner AD. Drug delivery from jet nebulisers. Arch Dis Child 1992; 67:586-591.

Everard ML, Hardy JG, Milner AD. Comparison of nebulised aerosol deposition in the lungs of healthy adults following oral and nasal inhalation. Thorax 1993; 48:1045-1046.

Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonisation with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol 1997; 23:330-335.

Geers TA, Baker NR. The effect of sublethal levels of antibiotics on the pathogenicity of *Pseudomonas aeruginosa* from tracheal tissue. J Antimicrob Chemother 1987; 19:569-578.

Govan JRW. Insights into cystic fibrosis microbiology from the European tobramycin trial in cystic fibrosis. J Cystic Fibrosis 2002; In Press.

Heinzi B, Eber E, Oberwaldner B, Haas G, Zach MS. Effects of inhaled gentamicin prophylaxis on acquisition of *Pseudomonas aeruginosa* in children with cystic fibrosis: a pilot study. Pediatr Pulmonol 2002; 33:32-37.

Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Lancet 1981; ii; 1137-1139.

Hodson ME, Gallagher CG, Govan JRW. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. Eur Respir J 2002; 20:658-664.

Hutchinson GR, Parker S, Pryor JA, Duncan-Skingle F, Hoffman PN, Hodson ME, et al. Home use nebulisers: a potential primary source of *Burkholderia cepacia* and other colistin resistant gram negative bacteria in patients with cystic fibrosis. J Clin Microbiol 1996; 34:584-587.

Jensen T, Pedersen SS, Garne S, Heilmann C, Hoiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. J Antimicrob Chemother 1987; 19:831-838.

Kerem E, Corey M, Gold R, Levison H. pulmonary function and clinical course in patients with cystic fibrosis after pulmonary colonisation with *Pseudomonas aeruginosa*. J Pediatr 1990; 116:714-719.

Kosorok MR, Zeng L, West SE, Rock MJ, Splaingard M, Laxova A, et al. Acceleration of lung disease after *Pseudomonas aeruginosa* acquisition. Pediatr Pulmonol 2000; Suppl 20:313.

Le Conte P, Potel G, Peltier P, Horeau D, Caillon J, Juvin ME, et al. Lung distribution and pharmokinetics of aerosolised tobramycin. Am Rev Respir Dis 1993; 147:1279-1282.

Ledson MJ, Gallagher MJ, Cowperthwaite C, Robinson M, Convery RP, Walshaw MJ. A randomised double blind placebo controlled crossover trial of nebulised taurolidine in adult CF patients colonised with *B. cepacia*. 22nd European CF Conference. Berlin, 1998. PS 5-17 page 120.

Littlewood J, Miller MG, Ghoneim AT, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet 1985; i:865.

Littlewood JM, Smye SW, Cunliffe H. Aerosol antibiotic treatment in cystic fibrosis. Arch Dis Child 1993; 68:788-792.

Maddison J, Dodd M, Webb AK. Nebulised colistin causes chest tightness in adults with cystic fibrosis. Respir Med 1994; 88:145-147.

Marsden RJ, Conway SP, Dodd ME, Edenborough FP, Paul EA, Rigby AS, et al. A multi-centre, randomised study comparing the Halolite adaptive aerosol delivery (AAD) system with a high output nebuliser system in patients with cystic fibrosis. European Cystic Fibrosis Society Meeting, Genoa, 2002.

McRorie T, Bosso J, Randolph L. Aminoglycoside ototoxicity in cystic fibrosis. Evaluation by high frequency audiometry. Am J Dis Child 1989; 143:1328-1332.

Moss RB. Long-term benefits of inhaled tobramycin in adolescent patients with cystic fibrosis. Chest 2002; 121:55-63.

Mukhopadhyay S, Singh M, Cater JI, Franklin M, Olver RE. Nebulised antipseudomonal antibiotic therapy in cystic fibrosis: a meta analysis of benefits and risks Thorax 1996; 51:364-368.

Newman SP, Woodman G, Clarke SW. Deposition of carbenicillin aerosols in cystic fibrosis: effects of nebuliser system and breathing pattern. Thorax 1988; 43:318-322.

Pamukcu A, Bush A, Buchdahl R. Effects of *Pseudomonas aeruginosa* colonisation on lung function and anthropometric variables in children with cystic fibrosis. Pediatr Pulmonol 1995; 19:10-15.

Pitchford KC, Corey M, Highsmith AK, Perlman R, Bannatyne R, Gold R, et al. Pseudomonas species contamination of cystic fibrosis patients' home inhalation equipment. J Pediatr 1987; 111:121-216.

Ramsey BW, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Kravitz RM, et al. Efficacy of aerosolised tobramycin in patients with cystic fibrosis. N Eng J Med 1993; 328:1740-6.

Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Eng J Med 1999; 340:23-40.

Ratjen F. Doring G. Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. Lancet 2001; 358:983-984.

Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotic therapy for cystic fibrosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Schaad UB, Wedgwood-Krucko J, Suter S, Kraemer R. Efficacy of inhaled amikacin as an adjunct to intravenous combination therapy (ceftazidime and amikacin) in cystic fibrosis. J Pediatr 1987; 111:599-605.

Smith AL, Ramsey BW, Hedges DL, Hack B, Williams-Warren J, Weber A, et al. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. Pediatr Pulmonol 1989; 7:265-271.

Stephens D, Garey N, Isles A, Levison H, Gold R. Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. Ped Infect Dis 1983; 2:209-211.

Taylor R, Hodson M. Cystic fibrosis: antibiotic prescribing practices in the United Kingdom. Eur Respir Med 1993; 7:535-540.

Valerius NH, Koch C Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. Lancet 1991; 338:725-726.

Wiesemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G. Placebo-controlled double blind randomized study of aerosolized tobramycin for early treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis. Pediatr Pulmonol 1998; 25:88-92.

Wilmott RW, Tyson SL, Matthews DJ. Cystic fibrosis survival rate: the influence of allergy and *Pseudomonas aeruginosa*. Am J Dis Child 1985; 139:669-671.

Yamagishi Y, Fujita J, Takigawa K, Negayama K, Nakazawa T, Takahara J. Clinical features of *Pseudomonas cepacia* pneumonia in an epidemic among immunocompromised patients. Chest 1993; 103:1706-09.

6. INTRAVENOUS ANTIBIOTICS

6.1 Indications for intravenous antibiotic therapy

Appropriate and early use of intravenous antibiotic therapy has been one of the main factors responsible for the improved prognosis for patients with cystic fibrosis (Wood & Piazza, 1988 [III]).

Intravenous antibiotics are used in the following circumstances –

- To eradicate early *P. aeruginosa* infection when combined oral and nebulised treatment has failed or is inappropriate.

- To treat new but mild respiratory symptoms and signs that have failed to clear with oral antibiotic therapy.

- To treat a respiratory exacerbation.

- As routine treatment for 2 weeks every 3 months of patients with chronic *P. aeruginosa* infection.

6.2 Eradication of early *Pseudomonas aeruginosa* infection

Aim. To delay and possibly prevent chronic *P. aeruginosa* infection by intensive treatment of the early infection.

Evidence. The Copenhagen CF Centre reported clearance of 80% of early infection *P. aeruginosa* infections with 3 weeks treatment with oral ciprofloxacin (250-750 mg twice-daily) and nebulised colistin (1 megaunit twice-daily) (Valerius et al, 1991 [Ib]). This protocol has been modified to a 3-month course of ciprofloxacin (25-50 mg/kg/day) and nebulised colistin (2 megaunits 3-times-daily) (Frederiksen et al, 1997 [IIb]). This prolongs the interval from eradication to reinfection from 9 to 18 months.

There are no data on the efficacy of intravenous antibiotics in eradicating *P. aeruginosa* infection from patients if 3 months of combined oral and nebulised therapy has failed to do so, yet clinical experience suggests that it may be successful in some patients.

Alternatives. When 3 weeks of oral ciprofloxacin and nebulised colistin have failed to eradicate early *P. aeruginosa* infection, it is reasonable to try a 2-week course of intravenous anti-Pseudomonal antibiotics and nebulised colistin as a more intensive and aggressive assault on this damaging pathogen. Intravenous antibiotics without nebulised colistin are reported to achieve successful eradication of *P. aeruginosa* infection in only 20% of patients (Steinkamp et al, 1989 [IV]) although many of these patients were not treated soon after the first positive culture and had been infected for a mean of 5 months (range 1 to 11 months). However, IV treatment alone in patients newly infected with *P. aeruginosa* is reported to have a high success rate (Munck et al, 2001 [III]).

Continuing the nebulised colistin for 12 months and carefully monitoring respiratory cultures, and (ideally) pseudomonal antibody levels, can prolong successful eradication. Any subsequent isolate could be treated with a further course of combined oral ciprofloxacin and nebulised colistin followed by intravenous antibiotic therapy with the nebulised colistin where the *P. aeruginosa* persists.

Children under 3 years could be started on nebulised colistin or tobramycin alone as both these are effective in eradicating early *P. aeruginosa* in many patients (Littlewood et al, 1985 [IV]; Weisemann et al, 1998 [Ib]; Ratjen et al 2001 [III]). If the cultures remain positive after 2 to 3 weeks, a course of intravenous antibiotics should be added to the nebulised colistin.

No patient should be allowed to develop chronic *P. aeruginosa* infection without having a trial of ciprofloxacin and nebulised colistin and, if this fails, a course of intravenous antibiotics and nebulised colistin. If this latter regimen fails the patient should continue with regular twice-daily nebulised colistin and have regular 2-week courses of intravenous antibiotics every 3 months or whenever respiratory symptoms and signs worsen. In a few patients the *P. aeruginosa* infection will clear and the pseudomonal antibodies will return to normal if they were raised.

Recommendations
- *Regular respiratory cultures, should be performed every 4 to 8 weeks and at times of increase in respiratory symptoms [C].*

- *At the first positive P. aeruginosa culture patients 3 years and older should receive 3 weeks of oral ciprofloxacin and nebulised colistin. Some clinicians would now continue the ciprofloxacin and colistin for 3 months even after the first episode of positive culture and even if the culture becomes negative at 3 weeks [B].*

- *Patients under 3 years should start nebulised colistin but, if the organism is not eradicated in 3 weeks, a course of intravenous antibiotics should be added to the nebulised treatment even if the patient appears well. Nebulised colistin and ciprofloxacin suspension is an alternative regimen for children under 3 years old and has been used without problems (see also Section 4.4) [B]. Some clinicians would recommend a course of IV antibiotics with the nebulised colistin at the first positive culture [C].*

6.3 Changes in clinical condition

Aim. To eradicate or stabilise pulmonary infection and prevent or minimise pulmonary damage.

Evidence. Anything other than an occasional mild cough in a child with CF indicates worsening of the respiratory infection.

The very early resort to intravenous antibiotic therapy to reverse new respiratory symptoms is one of the most important features of modern management.

The readiness to use IV antibiotics at an early stage of new symptoms, even when the patient is clinically well, differs considerably between Specialist CF Centres and CF Clinics being most commonly employed at Specialist CF Centres whose patients' respiratory function and nutrition lie within the upper quartiles (Wohl et al, 1998 [III]). In a previous study of US CF Centres, more frequent clinic attendances and more frequent use of intravenous antibiotics were associated with a much-improved survival (Wood & Piazza, 1988 [III]).

Recommendations
- *Even a mild cough, not previously present, should be treated with oral antibiotics covering infection with S. aureus, H. influenzae, Streptococcus pneumoniae, and, if appropriate, P. aeruginosa [B].*

- *A persistent cough not responding to supplementary oral antibiotic therapy is an indication for intravenous antibiotic treatment [C].*

- *If the cough and respiratory symptoms fail to respond to seemingly appropriate therapy, bronchoscopy and bronchoalveolar lavage should be considered and treatment altered, as appropriate to the lavage culture results (see also Section 3.5) [B].*

6.4 Treatment of an acute exacerbation

There is no universally agreed definition of a respiratory exacerbation. Most physicians will look for at least 4 of the following:

- increased productive cough or breathlessness
- changes in the appearance or volume of sputum
- new signs on auscultation
- new chest radiograph signs
- loss of appetite
- fall in respiratory function
- fever.

The most informative sign in patients old enough to perform respiratory function tests may be a fall of 10% or more from the base-line FEV_1 or FVC, plus increased severity of two or more lower respiratory tract symptoms (Pond & Conway, 1996a [III]).

Evidence. Pseudomonal antibody levels and various inflammatory markers can be used as indicators for intravenous treatment. In some patients the immunological response to new *P. aeruginosa* infection occurs very early, ocassionally before the organism can be reliably isolated (Brett et al, 1988 [III]; Brett et al, 1992 [IIb]). Antibody levels correlate well with the severity of the chest infection (Hoiby et al, 1977 [IIb]; Brett et al, 1986 [IIb]). They can be used as indicators for intravenous antibiotic treatment and for the frequency and intensity of such treatment, rising levels being early markers of worsening infection (Pond et al, 1994 [III]). Falling antibody levels are associated with clinical improvement (Brett et al, 1992 [IIb]).

Recommendations

- *There should be a low threshold of concern for starting intravenous antibiotic treatment [B].*

- *Intravenous antibiotic treatment should continue for a minimum of 10 days. Early treatment can prevent permanent loss of lung function, both in the short and intermediate term (Pond & Conway, 1996b [III]) [B].*

- *Pseudomonal antibody levels should be measured each year as part of the Annual Review also when P. aeruginosa is first isolated, and prior to treatment of an exacerbation in chronically infected patients. The results provide additional information to the cultures for the early detection of new P. aeruginosa infection and the early institution of therapy directed at its eradication [B].*

- *Rising Pseudomonal antibody levels in patients with established infection should be interpreted as an indication for intensifying treatment (Pond et al, 1994a [III]) [B].*

6.5 Elective three-monthly intravenous antibiotic therapy

Aim. To minimise any deterioration in clinical status resulting from chronic *P. aeruginosa* infection.

Evidence. It is recognised that clinical improvement is associated with a decrease in sputum

P. aeruginosa density (Smith et al, 1988 [III]; Regelman et al, 1990 [III]). In chronically infected patients, lung function gradually returns to pre-treatment levels within 1 to 3 months following a course of intravenous anti-pseudomonal antibiotic treatment. It seems logical to treat with antibiotics at regular intervals. At the Copenhagen CF Centre, following the introduction of a policy of regular 3-monthly intravenous antibiotic treatment, the 5-year survival of chronically infected patients increased from 54% to 82% (Szaff et al, 1983 [III]; Jensen et al, 1989 [III]; Frederiksen et al, 1997 [III]).

The positive effect on lung function must be set against the disruption of patients' lifestyles and the heightened risk of hypersensitivity reactions and of bacterial antibiotic resistance (Pedersen et al, 1986 [III]; Mouton et al, 1993 [IV]; Ciofu et al, 1994 [IV]). Home intravenous antibiotic programmes may counter the former concern. Resolution of the latter relies on time-consuming desensitisation procedures and the development of new anti-pseudomonal antibiotics, which are unlikely to be available in the next 10 years.

A 3-monthly IV antibiotic regimen has been adopted by a number of other Specialist CF Centres, although its value has not been established by a satisfactory controlled trial. In a recent study of adults with CF in the UK comparing 3-monthly and elective IV antibiotics, no advantage was apparent for those having regular 3-monthly treatment: in fact their mortality was slightly increased (Elborn et al, 2000 [Ib]). However, the numbers were small and the study generally regarded as underpowered; also patients in the elective group had no fewer than 3 courses of treatment per year, only 1 less than the patients receiving 3-monthly treatments.

A recent Cochrane Review concluded that the available studies were insufficient to identify conclusive evidence favouring a policy of elective intravenous antibiotic administration, despite its widespread use (Breen & Aswani, 2002 [Ia]).

A trial of regular IV therapy in patients starting soon after the onset of chronic *P. aeruginosa* infection is required rather than in those with advanced lung disease.

Recommendations

- *The potential advantages and disadvantages of routine elective intravenous antibiotic treatments should be explained to and discussed in detail with all parents/patients before deciding whether they are to have regular elective or 'on demand' intravenous treatment [C].*

- *Patients who have measurable deterioration in respiratory function between courses of IV antibiotics despite regular treatment, including nebulised antibiotics, should be considered for 3-monthly treatment [B].*

- *Those who are chronically infected, but whose condition and respiratory function are usually stable for prolonged periods on routine treatment (including regular inhaled antibiotics), could be treated with IV antibiotics only when they have a respiratory exacerbation [B].*

6.6 Choice of antibiotic

Aim. The primary aim is to achieve the most effective and least toxic treatment. Secondary aims are to reduce the likelihood of bacterial resistance and use the most cost-effective regimen.

Evidence. Two antibiotics should be used to reduce the risk of the development of antibiotic resistance, which has been associated with monotherapy and epidemic spread (Cheng et al, 1996 [III]). Although a meta-analysis of single versus combination antibiotic therapy did not

demonstrate significant differences in the clinical response to the 2 regimens, single therapy was associated with an increase in the number of patients with resistant strain of *P. aeruginosa* at the 2 to 8 weeks follow-up (Elphick & Tan, 2002 [Ia]). Combination antibiotic therapy is used, as *in vitro* studies have demonstrated a synergistic effect of a β-lactam and an aminoglycoside against *P. aeruginosa* isolates, even when there is resistance to an individual drug (Stratton & Tansk, 1987 [III]; Weiss et al, 1995 [III]). Although there have been many comparative short-term studies of different antibiotics, the most frequently used combination is ceftazidime and tobramycin. In adults with CF piperacillin/tazobactam plus tobramycin has been reported as effective treatment for infective exacerbations (Masterton et al, 2000 [IIb]). Because of the rapid clearance of drugs the antibiotic dose is high. There have been no health economic studies assessing the cost: benefit ratio of the more expensive intravenous antibiotics e.g. meropenem.

Recommendations
- *Two antibiotics should be used in combination for a course of intravenous therapy [B].*

- *The antibiotics should have a different mechanism of action e.g. an aminoglycoside and a β-lactam [B].*

- *The choice of antibiotic is determined by the sensitivity of the cultured P. aeruginosa. The growth of multiple strains or variants of Pseudomonas with different resistance patterns and other resistant bacteria such as B. cepacia and Stenotrophomonas maltophilia may confound this choice. However, each patient will have a portfolio of previous sputum or throat swab cultures, and effective antibiotics should be chosen for the sensitivity pattern of the most resistant organism [C].*

- *The optimum frequency of antibiotic delivery is currently debated. β-lactams are usually given 3-4 times a day, as their killing of P. aeruginosa is most effective when antibiotic levels are maintained above the MIC for prolonged periods of time. The blood levels of β-lactams need not be monitored. Aminoglycosides are traditionally given 3-times-daily but are increasingly given as a single daily dose, since their best effect is related to achieving intermittent high levels and their toxicity to failure to clear the drug adequately between doses [B].*

- *Two weeks treatment is usually given, but this need not be rigid. Attention to multiple parameters of clinical improvement is needed to help determine when maximal benefit has been realised e.g. respiratory function tests and oxygen saturation return to pre-exacerbation levels; levelling off of weight gain and scores of clinical wellbeing; normalisation or significant falls in inflammatory markers and the patient's subjective sense of the degree of improvement achieved [B].*

6.7 Practical aspects of intravenous antibiotic delivery

The mode of antibiotic delivery should ideally maximise antibacterial activity but may also have to fit in the with the patient's lifestyle. Patients with CF usually have or will develop poor venous access due to repeated courses of intravenous antibiotics damaging their veins. Venous access has been improved with the use and development of totally implantable venous access systems (TIVAS) (Stead et al, 1987 [IV]; Rodgers et al, 1998 [IV]). A surgeon experienced in their placement in patients with CF should insert them. These devices permit improved compliance and allow more IV therapy to be given at home. They need scrupulous care and regular, usually monthly, flushing with heparin saline using a full aseptic technique. Infection (usually staphylococcal or fungal) or blockages are the most common complications (Horn & Conway, 1993 [IV]; Burdon et al, 1998 [IV]).

6.8 Aminoglycoside dosing intervals

Aim. To realise the most effective and least toxic aminoglycoside dosage regimen.

Evidence. The standard dosage regimen for tobramycin or gentamicin in CF is 9-12 mg/kg/day divided into 3 equal doses. This differs from the amikacin dose of 30 mg/kg/day in 3 divided doses. The UK SPC (summary of product characteristics) data sheet provides information on dilutions for infusions and bolus administration, as well as on the timing and target levels for drug monitoring. The optimum peak serum level for tobramycin or gentamicin is 8 to 12 mg/l 30 minutes after completion of the intravenous infusion or 1 hour after bolus dosing and the optimum trough level is <1 mg/l. Suggested alterations to aminoglycoside dosage based on peak and trough levels are available (Lindsay & Bosso, 1993 [III]). It is essential that serum levels be monitored.

As aminoglycosides show concentration-dependent killing and as their toxicity depends on trough levels, once- or twice-daily administration has potential advantages over the standard 3-times-daily dose. In patients without CF, once-daily dosing has been shown to be as effective and less toxic than the 3-times-daily regimen (Barza et al, 1996 [Ia]). Reduced renal toxicity probably results from less renal tissue accumulation through saturation of the active transport mechanism that concentrates aminoglycosides in the renal cortex (Verpooten et al, 1989 [III]). There will also be drug-free periods towards the end of each dosing interval. Data on inner ear toxicity are scanty but there seems no greater problem with a once-daily compared with the 3-times-daily regimen (Nordstrom et al, 1990 [III]; Powell et al, 1983 [III]).

The higher peak levels achieved with the once-daily regimen result in higher antibiotic levels in CF sputum and an increased aminoglycoside bactericidal effect in the bronchial secretions, potentially enhancing treatment efficacy but there are few clinical studies in patients with cystic fibrosis. In adults with CF twice-daily dosing is equally effective as the standard 3-times-daily regimen; there was no renal toxicity and a lesser incidence of ototoxicity (Wood et al, 1996 [Ib]). In a retrospective study in 60 adult patients CF who received once-daily tobramycin 8 mg/kg/day for 100 respiratory exacerbations, there was good efficacy without renal or hearing problems (Whitehead et al, 1996 [IV]). In a further study of 60 adult patients equivalence was shown between once and 3-times-daily dosing with tobramycin where power of the study permitted (Whitehead et al, 2002 [Ib]). A study of 22 children with CF found once-daily tobramycin combined with 8 hourly ceftazidime to be safe and effective in treating pulmonary pseudomonas exacerbations (Vic et al, 1998 [IIb]). Tobramycin at 15 mg/kg infused over 30 minutes (Vic et al 1996 [IIb]; Canis et al, 1998 [IIb]), or 10 mg/kg over 1 hour (Gugliemo et al, 1996 [III]), or amikacin at 35 mg/kg infused over 30 minutes (Canis et al, 1997 [IIb]; Begg et al, 1995 [III]) have been shown to be safe and effective. Peak drug tobramycin levels were approximately 3 times greater with the once-daily dose. The amikacin sputum concentration remained above MIC_{50} (the concentration inhibiting *in vitro* growth of 50% of *P. aeruginosa* strains) for 16 hours after infusion. Serum levels can be predicted (Gugliemo et al, 1996 [III]). In practice, patients on a once-daily regimen are often monitored by measurement of trough aminoglycoside levels. There are no references to support the adequacy of this practice but a pre-dose measurement is practically easy and a level of <1 mg/l should be safe if repeated within the first week.

A recent Cochrane Review concluded that there was no difference in clinical outcome, nephrotoxicity or otoxicity between once and 3-times-daily dosing regimens but an adequately powered randomised controlled trial was required (Tan & Bunn, 2002 [Ia]).

Recommendations
- *The standard 3-times-daily dosing regimen of aminoglycosides is recommended for children with CF until the results of the UK multicentre trial of once-daily tobramycin are available*

(Smyth, 1999 [Ib]) [A]. Once-daily dosing is recommended for children if the UK multicentre trial confirms the safety of this regimen in children. Details available from Dr. Alan Smyth, Consultant Respiratory Paediatrician, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB [A].

● *For adults with CF, the once-daily dosing offers a real advantage during home intravenous treatment. With careful monitoring, a once-daily regimen can be used as an alternative to 3-times-daily dosing, although the results of ongoing trials should be carefully assessed [A].*

6.9 Problem areas
6.9.1 Different antibiotic resistance patterns

Several *P. aeruginosa* variants may be cultured from one sputum specimen, with different resistance patterns for each organism. Thus resistance can be partial but not total.

Recommendation
● *The appropriate strategy is to combine antibiotics so that at least 1 antibiotic is given to which each individual organism is sensitive [C].*

6.9.2 Pan-resistance to antibiotics

This is usually defined as resistance to all antibiotics in 2 of the following antibiotic classes; β-lactams, aminoglycosides and quinolones. Resistance to the polymyxins remains less frequent (Govan, 2002 [IIb]). Pan-resistance (except to colistin) most commonly occurs whilst patients are awaiting transplantation and will sometimes require frequent or continuous doses of intravenous antibiotics. Pan-resistance does not confer a worse prognosis for those patients with CF who receive a transplant (Aris et al, 1997 [III]).

Total antibiotic resistance in *B. cepacia*, in particular the epidemic form, is very common prior to transplantation. It can be a contraindication to transplantation.

Recommendations
● *A choice of intravenous antibiotics should be made according to previous best clinical response and the antibiotics should be rotated until a satisfactory response is achieved [C].*

● *Resistance to colistin is relatively uncommon in <u>P. aeruginosa</u> and it can be safely used intravenously (Conway et al, 1997 [Ib]; Conway et al, 2000 [IV]; Ledson et al, 1998 [IV]) [B]. In contrast, resistance of <u>B. cepacia</u> to colistin is total.*

● *Antibiotics can be tested in pairs for efficacy <u>in vivo</u>, to assess synergy against resistant organism (Saiman et al, 1996 [IIb]; Richards et al, 1998 [IIb]) [C].*

6.9.3 Allergic reactions (see also Section 10.)

Increasing drug allergy in patients with CF requiring repeated courses of antibiotics can severely limit choice by excluding antibiotics to which the patient's organisms are sensitive. Repeated courses of intravenous antibiotics through childhood to adulthood are associated with the development of allergic reactions, especially to the β-lactams, and with increasing disease severity. The commonest reactions are the development of rashes, but life-threatening anaphylactic reactions are not uncommon.

Recommendations

- *Drug allergy must be clearly documented in the patient's notes [C].*

- *Patients will be taught to self-inject adrenaline. An autoinjector for adults will deliver 0.3 mg per single dose (EpiPen) and should always be carried by very allergic patients. A 0.15 mg autoinjector is available for children [C].*

- *A patient having home IV antibiotic therapy should always be given the first and, ideally, the second dose of the antibiotic in hospital [C].*

- *It may be necessary to desensitise patients to antibiotics such as ceftazidime (Ghosal & Taylor, 1997 [IV]). This should always be carried out in hospital (see Section 10) [C].*

6.9.4 Pregnancy and antibiotics

In a large adult Specialist CF Centre (200 patients) it is usual for there to be at least 2 pregnancies each year (Edenborough et al, 2000 [IV]). If a pregnant patient is chronically infected with *P. aeruginosa* several courses of intravenous antibiotics may be required. Fortunately, the most useful intravenous antibiotics are safe (Lynch et al, 1991 [IV]).

Recommendations

- *The β-lactams (penicillins, cephalosporins and monobactams) can be safely used intravenously throughout pregnancy; intravenous colistin should be avoided [C].*

- *Safe oral antibiotics include erythromycin and clindamycin. Chloramphenicol, metronidazole and ciprofloxacin should be avoided [C].*

- *Aminoglycosides, which are the cornerstone of intravenous antibiotic therapy, are probably safe to use but levels should be carefully monitored. The potential for ototoxicity is greatest during the second trimester when the hair cells in the organ of Corti are developing. Foetal auditory changes may occur independently of maternal ototoxicity [C].*

6.10 Home intravenous antibiotic treatment

Aim. To administer intravenous antibiotic treatment with minimum disruption to the patient's and family's lifestyle, whilst maintaining equal efficacy to hospital-based programmes.

Evidence. Intravenous antibiotics administered to the patient at home can be as effective as hospital treatment and allow continued enjoyment of home comforts and the possibility of continuing with work or study (Winter et al, 1984 [III]; Strandvik et al, 1988 [III]; Gilbert et al, 1988 [IIa]; Strandvik et al, 1992 [III]; Pond et al, 1994b [IIa]; Wolter et al, 1997 [IIa]). The risks of cross-infection are reduced, and home treatment is also considerably less expensive than that in hospital (Wolter et al, 1997 [IIa]; Littlewood et al, 1995 [III]). A systematic Cochrane review of home intravenous antibiotics, although finding only one of the published studies acceptable, concluded that short-term home therapy does not seem to harm patients and in general reduced social disruptions. It was recommended that the decision to attempt home treatment should be based on an individual basis and appropriate local resources (Marco et al, 2002 [Ia])

Recommendations

- *It is essential that patients are carefully selected. The following prerequisites must be met; adequate facilities in the home, reliable adherence to therapy, a sensible and mature patient*

or parent, secure venous access, proper training in all appropriate techniques, and proper and continuing supervision [C].

● *Therapy should be made as patient-friendly as possible, by using bolus doses and/or pre-packed delivery devices and, where appropriate, once- or twice-daily doses [C].*

● *Patients should receive the first antibiotic dose at the hospital, either in the ward or the clinic. The first 2 doses should be given in hospital if the antibiotic is being used for the first time, to minimise the risk of an acute adverse event occurring at home [C].*

● *All patients should be supplied with a home anaphylaxis kit and its contents should be checked regularly. Adult patients, parents, family or partners should be instructed in its use [C].*

● *Patients receiving home intravenous antibiotics must have their progress assessed after 1 week's treatment and at the end of the course. These patients should be discussed during ward rounds in as much detail as the inpatients [C].*

● *Home therapy should be coordinated by the CF Nurse Specialist in conjunction with the CF Pharmacist and is not feasible without this level of support [C]. (See National Consensus Standards for the Nursing Management of Cystic Fibrosis. UK Cystic Fibrosis Nurse Specialist Group. Cystic Fibrosis Trust. 2001 [IV].)*

● *All Specialist CF Centres and Clinics should regularly review their home intravenous treatment outcomes, because not all such programmes are successful (Bradley et al, 1997 [III]) and patients may find it difficult to carry out other aspects of their treatment, especially physiotherapy and exercise (Phillips et al, 1997 [III]). Any patient failing to respond to a course of home treatment should be admitted and reviewed [C].*

● *Any complicated respiratory exacerbation e.g. with haemoptysis or pneumothorax should be treated in hospital [C].*

6.11 References

Aris RM, Gilligan PH, Neuringer IP, Gott KK, Rea J, Yankaskas JR. The effects of pan resistant bacteria in cystic fibrosis patients on lung transplant outcome. Am J Respir Crit Care Med 1997; 155:1699-1704.

Barza M, Ioannidis JPA, Cappelleri JC, Lau J. Single or multiple daily doses of aminoglycosides: a meta-analysis. BMJ 1996; 312:338-345.

Begg EJ, Barclay ML, Duffull SB. Suggested approach to once daily aminoglycoside dosing. Br J Clin Pharmacol 1995; 39:605-609.

Bradley JM, Wallace ES, Elborn JS, Howard JL, McCoy MP. The effects of intravenous antibiotic treatment on changes in spirometry in cystic fibrosis. Pediatr Pulmonol 1997; Suppl 14: A296.

Breen L, Aswani N. Elective versus symptomatic intravenous antibiotic therapy for cystic fibrosis (Cochrane Review). In: Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Brett MN, Ghonheim ATM, Littlewood JM. Serum antibodies to *Pseudomonas aeruginosa* in cystic fibrosis. Arch Dis Child 1986; 61:1114-1120.

Brett MN, Ghoneim ATM, Littlewood JM. Prediction and diagnosis of early *Pseudomonas aeruginosa* infection; a follow-up study. J Clin Microbiol 1988; 26:1565-1570.

Brett MN, Simmonds EJ, Ghoneim ATM, Littlewood JM. The value of serum IgG titres against *Pseudomonas aeruginosa* in the management of early infection in cystic fibrosis. Arch Dis Child 1992; 67:1086-1088.

Burdon J, Conway SP, Murchan P, Lansdown M, Kester RCK. Five years experience of PAS Port intravenous access system in adult cystic fibrosis. Eur Respir J 1998; 12:212-216.

Canis F, Husson MO, Turck D, Vic P, Ategbo S, Vincent A, et al. Pharmacokinetics and bronchial diffusion of single daily dose of amikacin in cystic fibrosis patients. J Antimicrob Chemother 1997; 39:431-433.

Canis F, Triver D, Vic P, Ategbo S, Turck D, Husson MO. Comparison of pharmacokinetics of tobramycin administered as a single daily dose or in three doses in cystic fibrosis. Pathol Biol (Paris) 1998; 46:449-451.

Cheng K, Smyth RI, Govan JRW, Doherty C, Winstanley C, Denning N, et al. Spread of β–lactam resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. Lancet 1996; 348:638-642.

Ciofu O, Giwercman B, Pedersen SS, Hoiby N. Development of antibiotic resistance in *Pseudomonas aeruginosa* during two decades of antipseudomonal treatment at the Danish Cystic Fibrosis Center. APMIA 1994; 102:674-680.

Conway SP, Pond MN, Watson A, Etherington C, Robey HL, Goldman MH. Intravenous colistin sulphomethate in acute respiratory exacerbations in adult patients with cystic fibrosis. Thorax 1997; 52:987-993.

Conway SP, Etherington C, Munday J, Goldman MH, Strong JJ, Wootton M. Safety and tolerability of bolus intravenous colistin in acute respiratory exacerbations in adults with cystic fibrosis. Ann Pharmacother 2000; 34:1238-1242.

Cystic Fibrosis Trust. National Consensus Standards for the Nursing Management of Cystic Fibrosis. UK Cystic Fibrosis Nurse Specialist Group. 2001.

Edenborough FP, Mackenzie WE, Stableforth DE. The outcome of 72 pregnancies in 55 women with cystic fibrosis in the United Kingdom 1977-1996. Brit J Obstet Gynecol 2000; 107:254-261.

Elborn JS, Prescott R, Stack B, Goodchild MC, Bates J, Pantin C, et al. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonas infection of the lungs. Thorax 2000; 55:355-358.

Elphick HE, Tan A. Single versus combination intravenous antibiotic therapy for people with cystic fibrosis (Cochrane review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonisation with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. Pediatr Pulmonol 1997; 32:330-335.

Ghosal S, Taylor CJ. Intravenous desensitisation to ceftazidime in cystic fibrosis patients. J Antimicrob Chemother 1997; 39:556-557.

Gilbert J, Robinson T, Littlewood J. Home intravenous antibiotic treatment in cystic fibrosis. Arch Dis Child 1988; 63:512-517.

Govan JRW. Insights into cystic fibrosis microbiology from the European tobramycin trial in cystic fibrosis. J Cystic Fibrosis 2002; In Press.

Guglielmo BJ, Quan LA, Stulbarg MS. Pharmacokinetics of once-v-thrice daily tobramycin in cystic fibrosis patients. J Antimicrob Chemother 1996; 37:1040-1042.

Hoiby N. Antibodies against *Pseudomonas aeruginosa* in serum from normal persons and patients colonised with mucoid or non-mucoid *P aeruginosa*: results obtained by crossed immunoelectrophoresis. Acta Pathol Microbiol Immunol Scand 1977; 85:142-148.

Horn CK, Conway SP. Candidaemia: risk factors in patients with cystic fibrosis who have totally implantable access systems. J Infect 1993; 26:127-132.

Jensen T, Pedersen SS, Hoiby N, Koch C, Flensborg EW. Use of antibiotics in cystic fibrosis. The Danish Approach. In: *Pseudomonas aeruginosa* infection. Antibiot Chemother. Hoiby N, Pedersen SS, Doring G, Holder IA, editors. Basel, Karger, 1989; 42:237-246.

Ledson MJ, Gallagher MJ, Cowperthwaite C, Convery RP, Walshaw MJ. Four years' experience of intravenous colomycin in an adult cystic fibrosis unit. Eur Respir J 1998; 12:592-4.

Littlewood JM, Miller MG, Ghoneim AT, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet 1985; i:865.

Littlewood JM on behalf of Glaxo Study Group. An audit to evaluate the costs of home vs hospital based treatment of cystic fibrosis patients. Thorax 1995; 50(Suppl 2): A38(S64).

Lindsay CA, Bosso JA. Optimisation of antibiotic therapy in cystic fibrosis patients pharmacokinetics considerations. Clin Pharmacokinet 1993; 24;496-506.

Lynch CM, Sinnott JT, Holt DA, Herold AH. Use of antibiotics during pregnancy. Clin Pharmacol 1991; 41:1365-1368.

Marco T, Asensio O, Bosque M, de Gracia J, Serra C. Home intravenous antibiotics for cystic fibrosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Masterton RG, Greening A, Rogers H, Range S, Legge JS, et al. A multicentre study of the safety and efficacy of piperacillin/tazobactam plus tobramycin in the treatment of respiratory exacerbations in adult cystic fibrosis patients. Bugs & Drugs 2000; 6:4.

Mouton JW, den Hollander JG, Horrevorts AM. Emergence of antibiotic resistance amongst *Pseudomonas aeruginosa* isolates from patients with cystic fibrosis. J Antimicrob Chemother 1993; 31:919-926.

Munck A, Bonacorsi S, Mariani-Kurkjian P, Lebourgeois M, Gerardin M, Brahimi N, et al. Genotype characterization of *Pseudomonas aeruginosa* strains recovered from patients with cystic fibrosis after initial and subsequent colonization. Pediatr Pulmonol 2001; 32:288-292.

Nordstrom L, Ringberg H, Cromberg S, Tjernstrom O, Walder M. Does administration of aminoglycoside in a single daily dose affect its efficacy and toxicity? J Antimicrob Chemother 1990; 25:159-173.

Pedersen SS, Koch C, Hoiby N, Rosendal K. An epidemic spread of multiresistant *Pseudomonas aeruginosa* in a cystic fibrosis centre. J Antimicrob Chemother 1986; 17:505-516.

Phillips AM, Abbott J, Webb AK. Effects of home intravenous treatment on other aspects of cystic fibrosis care. 21st European CF Conference, Davos, 1997. P167.

Pond MN, Carr I, Littlewood JM, Conway SP. A longitudinal study of anti-pseudomonas ELISA in young adults with cystic fibrosis. European CF Conference. Paris, 1994a. P24.

Pond MN, Newport M, Joanes D, Conway SP. Home vs. hospital intravenous antibiotic therapy in the treatment of cystic fibrosis. Eur Respir J 1994b; 7:1640-1644.

Pond MN, Conway SP. Towards a definition of pulmonary exacerbation for young adults with cystic fibrosis. Isr J Med Sci 1996a; 32:S243.

Pond MN, Conway SP. Treated pulmonary exacerbations in adults with cystic fibrosis do not result in loss of pulmonary function. Isr J Med Sci 1996b; 32:S243.

Powell SH, Thompson WL, Luthe MA, Stern RC, Grossniklaus DA, Bloxham DD, et al. Once daily vs. continuous aminoglycoside dosing efficacy and toxicity in animal and clinical studies of gentamicin, netilmicin and tobramycin. J Infect Dis 1983; 147:918-932.

Ratjen F. Doring G. Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. Lancet 2001; 358: 983-4.

Regelman WE, Elliott GR, Warwick WJ, Clawson CC. Reduction in sputum *Pseudomonas aeruginosa* density by antibiotics improves lung function in cystic fibrosis more than do bronchodilators and chest physiotherapy. Am Rev Respir Dis 1990; 141:914-921.

Richards RM, Hamilton VE, Thomas MR. *In vitro* investigation of the antibacterial activity of agents which may be used for the oral treatment of lung infections in CF patients. J Antimicrob Chemother 1998; 42:171-178.

Rodgers HC, Liddle K, Nixon SJ, Innes JA, Greening AP. Totally implantable venous access devices in cystic fibrosis: complications and patients' opinions. Eur Respir J 1998; 12:217-20

Saiman L, Mehar F, Niu WW, Shaw KJ, Miller G, Prince C. Antibiotic susceptibility of multiply resistant *Pseudomonas aeruginosa* isolated from patients with cystic fibrosis, including candidates for transplantation. Clin Infect Dis 1996; 23:532-537.

Smith AL, Redding G, Doershuk C, Goldmann D, Gore E, Hilman B, et al. Sputum changes associated with therapy for endobronchial exacerbation in cystic fibrosis. J Pediatr 1988; 112:547-554.

Smyth AR. A randomised controlled trial of once vs. thrice-daily tobramycin for pulmonary exacerbations of cystic fibrosis. CF Trust Project No.PJ467.1999.

Steinkamp G, Tummler B, Malottke R, von der Hardt. Treatment of *Pseudomonas aeruginosa* colonisation in cystic fibrosis. Arch Dis Child 1989; 64:1022-1028.

Stratton CW, Tansk F. Synergistic resistant mechanisms in *Pseudomonas aeruginosa*. Antimicrob Chemother 1987; 19:413-416.

Stead RJ, Davidson TI, Duncan FR, Hodson ME, Batten JC. Use of totally implantable system for venous access in cystic fibrosis. Thorax 1987; 42:149-150.

Strandvik B, Hjelte L, Widen B. Home intravenous antibiotic treatment in cystic fibrosis. Scand J Gastroenterol 1988; 23(Suppl 143): 119-120.

Strandvik B, Hjelte L, Widen B. Home intravenous antibiotic therapy treatment of patients with cystic fibrosis. Acta Paediatr 1992; 81:340-344.

Szaff M, Hoiby N, Flensborg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection. Acta Paediatr 1983; 72:651-657.

Tan K, Bunn H. Once daily versus multiple daily dosing with intravenous aminoglycosides for cystic fibrosis (Cochrane Review). In: The Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation by early treatment. Lancet 1991; 338:725-726.

Verpooten GA, Guiliano RA, Verbist L, Eatermans G Dr. Broe ME. Once daily dosing decreases accumulation of gentamicin and netilmicin. Clin Pharmacol Ther 1989; 45:22-27.

Vic P, Ategbo S, Turck D, Husson MO, Tassin E, Loeuiee GA, et al. Tolerance pharmacokinetics and efficacy of once daily amilkacin for treatment of *Pseudomonas aeruginosa* pulmonary exacerbations in cystic fibrosis patients. Eur J Pediatr 1996; 155:948-953.

Vic P, Ategbo S, Turck D, Husson MO, Launay V, Loeuille GA, et al. Efficacy, tolerance and pharmacokinetics of once daily tobramycin for pseudomonas exacerbations in cystic fibrosis. Arch Dis Child 1998; 78:536-539.

Weiss K, Lapointe JR. Routine susceptibility testing of four antibiotic combinations for improvement of laboratory guide to therapy of cystic fibrosis infections caused by *Pseudomonas aeruginosa*. Antimicrob Chemother 1995; 35:2411-2414.

Weisemann HG, Steinkamp G, Ratjen F, Bauernfeind A, Przyklenk B, Doring G, et al. Placebo-controlled, double-blind randomised study of aerosolised tobramycin for early treatment of *Pseudomonas aeruginosa* colonization in cystic fibrosis. Pediatr Pulmonol 1998; 25:88-92.

Whitehead A, Conway SP, Dave J. Once daily administration of tobramycin in an effective and safe treatment of acute respiratory exacerbations in adults with cystic fibrosis. Isr J Med Sci 1996; 32:S257.

Whitehead A, Conway SP, Etherington C, Calkdwell NA, Setchfield N, Bogle S. Once-daily tobramycin in the treatment of adult patients with cystic fibrosis. Eur Respir J 2002; 19:303-309.

Winter RJD, George RJS, Deacock SJ, Shee CD, Geddes DM. Self-administered home intravenous antibiotic therapy in bronchiectasis and cystic fibrosis. Lancet 1984; I: 1338-1339.

Wohl ME, Butler SM, Johnson CA. Measuring outcomes in ESCF: can we do it? Pediatr Pulmonol 1998; Suppl 17:148-149.

Wolter JM, Bowler SD, Nolan PJ, McCormack JG. Home intravenous therapy in cystic fibrosis: a prospective randomised trial examining clinical, quality of life and cost aspects. Eur Respir J 1997; 10:896-900.

Wood RE, Piazza F. Survival in cystic fibrosis: correlation with treatment in three cystic fibrosis centres. 10th International Cystic Fibrosis Congress, Sydney 1988. Excerpta Medica Asia Pacific Congress Series 74 Page 79.

Wood PJ, Ioannides-Demos LL, LiSC, Williams TJ, Hickey B, Spicer WJ, et al. Minimisation of aminoglycoside toxicity in patients with cystic fibrosis. Thorax 1996; 51:369-373.

7. OTHER INFECTIONS

7.1 Methicillin-resistant *Staphylococcus aureus*
7.1.1 General

A study from the Adult CF Unit, Royal Brompton Hospital, London reported 26 of 974 patients attending there between 1965 and 1997 were colonised with methicillin-resistant *Staphylococcus aureus* (MRSA). Such MRSA colonisation was without serious consequences for most patients with CF and the hospital infection control policies appeared to be successful in keeping its incidence low (Thomas et al, 1998 [IV]). People with CF probably acquire the MRSA strains that are present in their particular hospital. Control measures are important, as MRSA seriously compromises the choice of antibiotic treatment (Govan, 2000 [IV]). Methicillin-resistant *Staphylococcus aureus* are resistant to all β-lactam antibiotics and often to other agents including aminoglycosides and macrolides (Leski et al, 1999 [IV]).

A consensus meeting (Meeting Report, 1998 [IV]) concluded that MRSA does not currently appear to increase morbidity or mortality in CF, although further research was needed. The infection did however cause considerable difficulties when patients were being considered for transplantations because of the consequences in the transplanted patients and also the risk of spread to other patients in intensive care units. Some Specialist CF Centres will not list patients with MRSA for transplant. Hospitals should follow national guidelines for the control of MRSA (Report of a Combined Working Party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association 1998 [IV]). 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. Patients with CF who are colonised/infected should be advised not to attend meetings or social gatherings of people with cystic fibrosis.

7.1.2 Treatment

The treatment alternatives are either antibiotics to which resistance frequently develops (e.g. fucidin and rifampicin), or are expensive and require intravenous administration (teicoplanin and vancomycin). All the MRSA isolates at the Royal Brompton Hospital, London, were sensitive to vancomycin and teicoplanin, 81% were susceptible to rifampicin, 77% to fucidin and 17% to erythromycin. Sensitivities were similar pre- and post-1992 (Thomas et al, 1998 [IV]). Recently linezolid, a new antibiotic of the oxazolidinone class that is active against gram-positive bacteria including both methicillin-susceptible and methicillin-resistant *S. aureus*, has been shown to be highly effective by both the intravenous and oral routes in a patient with CF with severe exacerbations of her chest infection due to MRSA (Ferrin et al, 2002 [IV]).

Recommendations
- *Regular monitoring of all patients with CF for MRSA [C].*

- *Arrange for the family to be screened and, if positive for MRSA, arrange treatment to eradicate [C].*

- *Treatment of nasal carriage is best achieved with nasal mupirocin (Hill et al, 1988 [III]), although resistance can arise.*

- *Follow hospital isolation policies (Report of a Combined Working Party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association 1998 [IV]) [C].*

- *Treat the MRSA, noting antibiotic sensitivities. If it is suspected that MRSA is causing symptoms try nebulised vancomycin 5 mg/kg tds or qds made up with 4 ml saline (Maiz et al, 1998 [IV]). Give nebulised salbutamol before the vancomycin. For acute exacerbations always include intravenous teicoplanin or vancomycin [C].*

- *Chronically infected patients are kept on long-term oral antibiotics to keep the bacterial count as low as possible. Inhaled aminoglycosides or oral agents are given for chronic sputum infection [C].*

- *Chloramphenicol may be used for acute exacerbations but not for long-term treatment. Many MRSA are resistant to chloramphenicol [C].*

- *Linezolid (Zyvox) shows promise but there is only one case report in a patient with cystic fibrosis who received 600 mg intravenously twice-daily. Suggested dose for patients over 5 years is 10 mg/kg twice-daily; patients less than 5 years 10 mg/kg 3-times-daily. Levels can be used to monitor dosing. Both oral and intravenous preparations are available (see Pharmacopoeia Section 9.3) [C].*

7.1.3 References

Ferrin M, Zuckerman JB, Meagher A, Blumberg EA. Successful treatment of methicillin-resistant *Staphylococcus aureus* pulmonary infection with linezolid in a patient with cystic fibrosis. Pediatr Pulmonol 2002; 33:221-223.

Govan JR. Infection control in cystic fibrosis: methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and the *Burkholderia cepacia* complex. J R Soc Med 2000; 93 (Suppl 38):40-45.

Hill RLR, Duckworth GJ, Casewell MW. Elimination of nasal carriage of methicillin resistant *Staphylococcus aureus* with mupirocin during a hospital outbreak. J Antimicrob Chemother 1988; 22:377-384.

Leski TA, Griadkowski M, Skoczynsk A, Stefanuick E, Trzcinski K, Hryiewicz W. Outbreak of mupirocin-resistant staphylococci in a hospital in Warsaw, Poland due to plasmid transmission and clonal spread of several strains. J Clin Microbiol 1999; 37:2781-2788.

Maiz L, Canton R, Mir N, Baquero F, Escobar H. Aerosolized vancomycin for the treatment of methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis. Pediatr Pulmonol 1998; 26:287-289.

Meeting Report. MRSA in cystic fibrosis. J Hosp Infect 1998; 40:179-191.

Report of a Combined Working Party of the British Society for Antimicrobial Chemotherapy, the Hospital Infection Society and the Infection Control Nurses Association. Revised guidelines for control of methicillin-resistant *Staphylococcus aureus* infection in hospitals. J Hosp Infect 1998; 39:253-290.

Thomas SR, Gyi KM, Gaya H, Hodson ME. Methicillin-resistant *Staphylococcus aureus*: impact at a national cystic fibrosis centre. J Hosp Infect 1998; 40:203-209.

7.2 *Stenotrophomonas maltophilia*

Isolation of *S. maltophilia* from sputa of patients with CF has increased markedly since the early 1980s (Gladman et al, 1992 [III]) and some Specialist CF Centres now report a prevalence of over 20% (Ballestero et al, 1995 [III]; Denton et al, 1996 [III]). 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 (Denton et al, 1996 [III]; Talmaciu et al, 2000 [III]; Valdezate et al, 2001 [IV]). 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 (Denton et al, 1998 [III]). Equipment used to deliver aerosolised antibiotics may be a potential source of *S. maltophilia* (Hutchinson et al, 1996 [III]). There is no evidence of patient-to-patient transmission (Denton et al, 1998 [III]; Krewinski et al, 2001 [III]; Vu-Thein et al, 1996 [III]) 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 patients (Karpati et al, 1994 [III]), although other studies have not shown this relationship (Gladman et al, 1992 [III]; Demko et al, 1995 [III]; Demko et al, 1998 [III]; Valdezate et al, 2001 [III]).

There are anecdotal reports that gradual deterioration only occurs in those patients colonised with >10^6 cfu of *S. maltophilia* per ml of sputum (Ballestero et al, 1995 [III]).

Unfortunately *S. maltophilia* is resistant to most anti-pseudomonal antibiotics (Denton & Kerr, 1998 [IV]). Only co-trimoxazole appears to have consistent activity but minocycline, ticarcillin/clavulanate or aztreonam plus co-amoxiclav may also be active. Combination therapy with ceftazidime plus an aminoglycoside or ciprofloxacin has been shown to be synergistic *in vitro* against some strains of *S. maltophilia*. Recent *in vitro* studies have also suggested that azithromycin may be synergistic in combination with cotrimoxazole against 20% of *S. maltophilia* strains isolated for patients with cystic fibrosis (Saiman et al, 2002 [III]).

Recommendations

- *Given the continuing doubts about clinical significance and the potential toxicity of the above 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 [C].*

- *Unless contra-indicated by resistance or intolerance, co-trimoxazole is the usual drug of choice [C]. Ticarcillin/clavulanate is another option [C].*

7.2.1 References

Ballestero S, Virseda I, Escobar H, Suarez L, Baquero F. *Stenotrophomonas maltophilia* in cystic fibrosis patients. Eur J Clin Microbiol Infect Dis 1995; 14:728-729.

Demko C, Doershuk C, Stern R. Thirteen year experience with *Xanthomonas maltophilia* in patients with cystic fibrosis. Pediatr Pulmonol 1995; Suppl 12:244.

Demko CA, Stern RC, Doershuk CF. *Stenotrophomonas maltophilia* in cystic fibrosis: incidence and prevalence. Pediatr Pulmonol 1998; 25:304-308.

Denton M, Todd NJ, Littlewood JM. Role of anti-pseudomonal antibiotics in the emergence of *Stenotrophomonas maltophilia* in cystic fibrosis patients. Eur J Clin Microbiol Infect Dis 1996; 15:402-405.

Denton M, Kerr KG. Microbiological and clinical aspects of infection associated with *Stenotrophomonas maltophilia*. Clin Microbiol Rev 1998; 11:57-80.

Denton M, Todd NJ, Kerr KG, Hawkey PM, Littlewood JM. Molecular epidemiology of *Stenotrophomonas maltophilia* isolated from clinical specimens of patients with cystic fibrosis and associated environmental samples. J Clin Microbiol 1998; 36:1953-1958.

Gladman G, Connor PJ, Williams RF, David TJ. Controlled study of *Pseudomonas cepacia* and *Pseudomonas maltophilia* in cystic fibrosis. Arch Dis Child 1992; 67:192-195.

Hutchinson GR, Parker S, Pryor JA, Duncan-Skingle F, Hoffman PN, Hodson ME, et al. Home-use nebulisers: a potential primary source of *Burkholderia cepacia* and other colistin-resistant gram-negative bacteria in patients with cystic fibrosis. J Clin Microbiol 1996; 34:584-587.

Karpati F, Malmborg A-S, Alfredsson H, Hjelte L, Strandvik B. Bacterial colonisation with *Xanthomonas maltophilia* – a retrospective study in a cystic fibrosis population. Infection 1994; 22:258-263.

Krewinski JW, Nguyen CD, Foster JM, Burns JL. Use of random amplified polymorphic DNA PCR to examine epidemiology of *Stenotrophomonas maltophilia* and *Achromobacter (Alcaligenes) xylosoxidans* from patients with cystic fibrosis. J Clin Microbiol 2001; 39:3597-3602.

Saiman L, Chen Y, San Gabriel P, Knirsch C. Synergistic activities of macrolides antibiotics against *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Alcaligines xylosoxidans* isolated from patients with cystic fibrosis. Antimicrob Agents Chemother 2002; 46:1105-1107.

Talmaciu I, Varlotta L, Mortensen J, Schidlow DV. Risk factors for emergence of *Stenotrophomonas maltophilia* in cystic fibrosis. Pediatr Pulmonol 2000; 30:10-15.

Valdezate S, Vindel A, Maiz L, Baquero F, Escobar H, Canton R. Persistence and variability of *Stenotrophomonas maltophilia* in cystic fibrosis patients, Madrid, 1991-1998. Emerging Infectious Diseases 2001; 7:113-122.

Vu-Thein H, Moissenet D, Valcin M, Dulot C, Tournier G, Garbag-Chenon A. Molecular epidemiology of *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and *Alcaligenes xylosoxidans* in a cystic fibrosis centre. Eur J Clin Microbiol Infect Dis 1996; 15:876-879.

7.3 Non-tuberculous mycobacteria

7.3.1 Clinical significance of non-tuberculous mycobacteria isolates in the 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. It is not possible to determine whether the organisms are contaminants, merely colonising the patient's airways, or represent a true infection. There is no consistent evidence that antibiotic treatment is beneficial.

7.3.2 Prevalence of non-tuberculous mycobacteria

Patients with chronic suppurative lung disease are potential subjects for non-tuberculous mycobacteria. 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 (Oerman et al, 1997 [IV]; Torrens et al, 1998 [III]; Hjelte et al, 1990 [III]; Kilby et al, 1992 [III]; Aitken et al, 1993 [III]; Fauroux et al, 1997 [III]). Non-tuberculous mycobacteria are found in the respiratory secretions of up to 20% of patients with CF, if appropriate isolation methods are used (Jones et al, 1995 [III]).

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 12.5% (123/986) which varied between CF clinics from 5%-31%; 2.5% (25/986) of patients fulfilled the American Thoracic Society's criteria of either 2 positive cultures and a positive smear or 3 positive cultures. *Mycobacterium avium* was cultured most frequently (77%) with *Mycobacterium abscessus* being the next most common (18%). The patients with positive cultures were older and had relatively mild chest involvement but worse nutritional status, were more likely to have *S. aureus* and tended towards being less likely to have *P. aeruginosa* than NTM culture negative patients (Oliver, 1999 [III]).

7.3.3 Evidence for pathogenicity

Although infiltrations and cavities in the chest X-ray, cough, haemoptysis, weight loss and a low-grade fever may all be due to conventional *P. aeruginosa* infection, they also may be due, at least in part, to active NTM infection. In most cases, it is unlikely that NTM infection is responsible (Tomashefski et al, 1996 [III]).

Some studies highlight the potentially pathologic effects of NTM in CF (Hjelte et al, 1990 [III]; Kilby et al, 1992 [III]; Boxerbaum, 1980 [III]; Kinney et al, 1989 [IV]; Smith et al, 1984 [III]; Efthimiou et al, 1984 [IV]) whilst others argue against any significant impact (Torrens et al, 1998 [III]; Aitken et al, 1993 [III]; Hjelt et al, 1994 [III]). One positive sputum culture is unlikely to be of significance, but active NTM infection should be suspected when multiple smears and cultures are positive for NTM (Tomashefski et al, 1996 [III]). Bronchoscopy, with endobronchial or

transbronchial biopsy, may be appropriate in some cases, with the presence of granulomata confirming active NTM disease.

7.3.4 Clinical and radiological features

The American Thoracic Society (ATS) criteria for active NTM infection illustrate the difficulties in making this diagnosis in cystic fibrosis (Wallace et al, 1996 [IV]). It is recommended that all other reasonable causes for clinical presentations are excluded, an impossibility in the case of CF, where other potential pathogens are generally present.

7.3.5 Treatment

Non-tuberculous mycobacteria are almost always resistant *in vitro* to standard anti-tuberculous antibiotics. Ethambutol should not be used in children too young to report adverse effects on vision. Clarithromycin and ciprofloxacin have some activity against NTM (Fauroux et al, 1997 [III]; McKean et al, 1992 [IV]). Treatment is usually given for 12 to 18 months.

Patients may improve with treatment (Torrens et al, 1997 [III]; Hjelte et al, 1990 [III]; Oliver et al, 2001 [IV]) or may not (Torrens et al, 1997 [III]; Hjelte et al, 1994 [III]). Even eradication of NTM does not guarantee clinical improvement (Fauroux et al, 1997 [III]).

The decision to treat is usually based on the clinical situation, deterioration in the presence of NTM, and with failure to respond to therapy for conventional CF respiratory pathogens. Conclusions about NTM disease or colonisation should be made on the basis of the host response to treatment.

Recommendations
- *Screen all patients with CF for mycobacteria at their Annual Review [C].*

- *The decision to treat is based on clinical grounds. Treat patients who are deteriorating and unresponsive to treatment for conventional CF respiratory pathogens, and who have repeatedly positive cultures or smears for non-tuberculous mycobacteria [C].*

- *Continue the antibiotic treatment for 12 to 18 months [C].*

- *Consider monitoring drug levels if sputum fails to become negative (Gilljam et al, 1999 [IV]) [C].*

7.3.6 References

Aitken ML, Burke W, McDonald G, Wallis C, Ramsay B, Nolan C. Non-tuberculous mycobacterial disease in adult cystic fibrosis patients. Chest 1993; 103:1096-1099.

Boxerbaum B. Isolation of rapidly growing mycobacteria in patients with cystic fibrosis. J Pediatr 1980; 96:689-691.

Efthimiou J, Smith MJ, Hodson ME, Batten JC. Fatal pulmonary infection with *Mycobacterium fortuitum* in cystic fibrosis. Br J Dis Chest 1984; 78:299-302.

Fauroux B, Delaisi B, Clement A, Saizou C, Moissenet D, Truffot-Pernot C, et al. Mycobacterial lung disease in cystic fibrosis: a prospective study. Pediatr Infect Dis J 1997; 16:354-358.

Gilljam M, Berning SE, Peloquin CA, Strandvik B, Larsson LO. Therapeutic drug monitoring in patients with cystic fibrosis and mycobacterial disease. Eur Respir J 1999; 14:347-51.

Hjelte L, Petrini B, Keallenius G, Strandvik B. Prospective study of mycobacteria in adult patients with cystic fibrosis. Thorax 1990; 45:397-400.

Hjelt K, Hojlyng N, Howitz P, Illum N, Munk E, Valerius NH, et al. The role of mycobacteria other than tuberculosis in patients with cystic fibrosis. Scand J Infect Dis 1994; 26:569-576.

Jones BJ, Fiaz ARM, Gilbert RE, Oliver KN. Multicenter investigation of non-tuberculous mycobacteria in patients with cystic fibrosis; update. Pediatr Pulmonol 1995; Suppl 12:P249 A245.

Kilby JM, Gilligan PH, Yankaskas JR, Highsmith WE, Edwards LJ. Non-tuberculous mycobacteria in adult patients with cystic fibrosis. Chest 1992; 102:70-75.

Kinney JS, Little BJ, Yolken RH, Rosenstein BJ. *Mycobacterium avium* complex in a patient with cystic fibrosis: disease vs. colonisation. Pediatr Infect Dis J 1989; 8:393-396.

McKean LP, Weber AG, Buchanan CN, Caplan DB. Mycobacterium infections in cystic fibrosis patients. Pediatr Pulmonol 1992; Suppl 8:P293 A217.

Oerman CM, Starje JR, Seilheimer DK. Pulmonary disease caused by *Mycobacterium kansaii* in a patient with cystic fibrosis. Pediatr Infect Dis J 1997; 16:257-259.

Oliver KN, for the NTM CF Study Group. Collaborative CFF/NCRR study of the epidemiology of non-tuberculous mycobacteria in cystic fibrosis. Pediatr Pulmonol 1999; Suppl 19:145-146.

Oliver A, Maiz L, Canton R, Escobar H, Baquero F, Gomez-Mampaso E. Non-tuberculous mycobacteria in patients with cystic fibrosis. Clin Infect Dis 2001; 32:1298-1303.

Smith MJ, Efthimiou J, Hodson ME, Batten JC. Mycobacterial isolations in young adults with cystic fibrosis. Thorax 1984; 39:369-375.

Tomashefski JF Jr., Stern RC, Demko CA, Doershuk CF. Non-tuberculous mycobacteria in cystic fibrosis: an autopsy study. Am J Respir Crit Care Med 1996; 154:523-528.

Torrens JK, Dawkins P, Conway SP, Moya E. Non-tuberculous mycobacteria in cystic fibrosis. Thorax 1998; 53:182-185.

Wallace RJ, O'Brien R, Glassroth J, Raliegh J, Dutt A. Diagnosis and treatment of disease caused by non-tuberculous mycobacteria. Am Rev Respir Crit Care Med 1996; 142:940-953.

7.4 Management of respiratory exacerbations in patients with *Burkholderia cepacia*

The outcome of *B. cepacia* complex 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 a 'cepacia syndrome' (Whiteford et al, 1995 [IV]; Muhdi et al, 1996 [IV]; Hutchison & Govan, 1999 [IV]; McLoskey et al, 2001 [IV]). In addition, patients with *B. cepacia* infection have more frequent exacerbations with secondary infecting organisms such as *P. aeruginosa*, *S. aureus* and *H. influenzae*. Accurate sputum culture is important to determine which antibiotics are most appropriate for each exacerbation.

Management of *B. cepacia* infection requires awareness of problems that may arise in culture and identification, including the consequences of recent taxonomic advances (Govan et al, 1996 [III]; LiPuma, 1998 [III]; Jones et al, 2001 [IV]; Coenye et al 2001 [III]). Briefly, isolates presently identified as '*B. cepacia*' by conventional methods comprise at least 9 bacterial species or subspecies. These include genomovars I, III and IV, and the newly described species *Burkholderia multivorans* and *Burkholderia vietnamiensis* (previously genomovars II and V). Because of their phenotypic similarity, and until the virulence of individual groups is clarified, all should be referred to as the *B. cepacia* complex. Within the complex, the distribution of isolates is disproportionate with almost 90% of isolates belonging to *B. multivorans* or genomovar III (LiPuma et al, 2001 [III]). Most organisms within the *B. cepacia* complex are inherently resistant to antipseudomonal antibiotics (Lewin et al, 1993 [III]; Pitt et al, 1996 [III]; Saiman, 1998 [III]). However, some groups such genomovar I, *B. multivorans* and *B. vietnamiensis* may be more sensitive, compared with genomovar III strains. Antimicrobial therapy should be directed by *in vitro* sensitivities where available, but many organisms are pan-resistant to the usual antibiotics. There is some value in checking minimal inhibitory concentrations (MICs) for such organisms. Reasonable MICs to antipseudomonal antibiotics such as ceftazidime, meropenem, temocillin and tazobactam can be demonstrated. In addition, co-trimoxazole, chloramphenicol, ciprofloxacin and individual tetracyclines may also show some activity against *B. cepacia* (Nzula et al, 2002 [III]; Moore et al, 2001 [III]).

It is preferable to use a combination of 2 or 3 antibiotics for treatment of *B. cepacia* exacerbations. Some combinations show synergy. Quinolones in combination with β-lactams or carbopenems may have some utility in this context. Other potentially synergistic combinations include chloramphenicol/minocycline and chloramphenicol/ceftazidime (Saiman, 1998 [III]; Aaron et al, 2000 [III]). It is hoped to provide further guidelines on synergy testing for treatment of resistant organisms such as *B. cepacia* in the near future.

Burkholderia cepacia is characteristically resistant to colistin and polymyxin and, in general, to aminoglycosides; although, the latter may be useful in combinations. It should also be remembered that some antibiotic combinations can be antagonistic. If a patient is not responding to antimicrobial therapy, further tests and possibly a change in the antibiotic regimen should be considered.

[See also Sections 9.10 - 9.12]

7.4.1 References

Aaron SD, Ferris W, Henry DA, Speert DP, MacDonald NE. Multiple combination bacterial antibiotic testing for patients with cystic fibrosis infected with *Burkholderia cepacia*. Am J Crit Care Med 2000; 161:1206-1212.

Coenye T, Vandamme P, Govan JRW, LiPuma JJ. Taxonomy and identification of *Burkholderia cepacia* complex. J Clin Microbiol 2001; 3427-3436.

Govan JRW, Hughes JE, Vandamme P. *Burkholderia cepacia*: medical, taxonomic and ecological issues. J Med Microbiol 1996; 45:395-407.

Hutchison ML, Govan JRW. Pathogenicity of microbes associated with cystic fibrosis. Microbes and Infection 1999; 1:1005-1014.

Jones AM, Dodd ME, Webb AK. *Burkholderia cepacia*: current clinical issues, environmental controversies and ethical dilemmas. Eur Respir J 2001; 17:295-301.

Lewin C, Doherty C, Govan JRW. In *vitro* activities of meropenem, PD 127391, PD 131628, ceftazidime, chloramphenicol, co-trimoxazole and ciprofloxacin against *Pseudomonas cepacia*. Antimicrob Agents Chemother 1993; 37:123-1254.

LiPuma JJ. *Burkholderia cepacia*: management issues and new insights. Clin Chest Med 1998; 19:473-4486.

LiPuma JJ, Spilker T, Gill LH, Campbell PN, Liu L, Mahenthiralingam E. Disproportionate distribution of *Burkholderia cepacia* complex species and transmissibility markers in cystic fibrosis. Am J Resp Crit Care Med 2001; 164:92-96.

McLoskey M, McCaughan J, Redmond AO, Elborn JS. Clinical outcome after acquisition of *Burkholderia cepacia* in patients with cystic fibrosis. Irish J Med Sci 2001; 170:28-31.

Moore JE, Crowe M, Shaw A, McCaughan J, Redmond AOB, Elborn JS. Antibiotic resistance in *Burkholderia cepacia* at two regional cystic fibrosis centres in Northern Ireland: is there a need for synergy testing. J Antimicrob Chemother 2001; 48:319-321.

Muhdi K, Edenborough FJ, Gumery L, O'Hickey S, Smith EG, Smith DL, et al. Outcome for patients colonised with *Burkholderia cepacia* in a Birmingham Cystic Fibrosis Clinic at the end of an epidemic. Thorax 1996; 51:374-377.

Nzula S, Vandamme P, Govan JRW. Influence of taxonomic status on the in *vitro* susceptibility of *Burkholderia cepacia* complex. J Antimicrob Chemother 2002; 50:265-269.

Pitt TL, Kaufmann ME, Patel PS, Benge LCA, Gaskin S, Livermore DM. Type characterization and antibiotic susceptibility of *Burkholderia (Pseudomonas) cepacia* isolates from patients with cystic fibrosis in the United Kingdom and the Republic of Ireland. J Med Microbiol 1996; 44: 203-210.

Saiman L. Antimicrobial resistance among Burkholderia, Stenotrophomonas, and Alcaligenes isolates studied by the CF Referral Center for susceptibility and synergy testing. Pediatr Pulmonol 1998; Suppl 17: 118-119.

Whiteford ML, Wilkinson JD, McColl JS, Conlon FM, Michie JR, Evans TJ, et al. Outcome of *Burkholderia (Pseudomonas) cepacia* colonisation in children with cystic fibrosis following a hospital outbreak. Thorax 1995; 50:1194-1198.

7.5 Allergic bronchopulmonary aspergillosis
7.5.1 Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is an immune-mediated bronchial disease causing bronchiectasis as a result of exposure to *Aspergillus fumigatus*. 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 (el-Dahr et al, 1994 [III]). 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. The successful treatment of *S. aureus* and early *P. aeruginosa* seems to increase the likelihood of respiratory cultures becoming positive for *A. fumigatus* (Bargon et al, 1999 [III]).

7.5.2 Diagnosis and recommendations

There should be a low threshold of suspicion for diagnosis, which is based on the following:

● The occurrence of asthma symptoms.

● New X-ray changes such as patchy atelectasis, consolidation, homogenous bronchial shadowing or parallel "tram line" linear shadows.

● Increased IgE levels of >500IU/L or a four-fold increase in IgE titres (Marchant et al, 1994 [III]).

● Increased specific IgE RAST or positive skin prick tests.

● Eosinophilia of >500/mm³.

● Positive sputum culture or fungal hyphae identified on microscopy.

Radiological and clinical improvements with a falling IgE level after initiating steroids usefully indicates an appropriate diagnosis (Simmonds et al, 1990 [III]).

Recommendations
● *Oral prednisolone 0.5 mg to 1 mg/kg (non-enteric coated) should be given daily for at least 2 weeks. If improvements in clinical symptoms, respiratory function tests and radiological changes have occurred after 2-3 weeks, give 0.5 mg to 1 mg/kg prednisolone on alternate days for the next 2-3 months [B].*

● *A resolution of symptoms, a return of respiratory function to previous levels, resolution of X-ray changes and a fall in total IgE of >35% by 2 months is indicative of remission (Ricketti et al, 1984 [III]) [B].*

● *If IgE levels are not reduced, consider whether there is poor adherence to the steroid therapy, and review the diagnosis. An absence of even mild Cushingoid facial changes when taking 1 mg/kg/day or more of oral prednisolone suggests either non-adherence or poor absorption – or perhaps the inadvertent prescription of an enteric coated preparation (Gilbert & Littlewood, 1986 [IV]). If the diagnosis is certain, a week or two of 2 mg/kg/day prednisolone may be effective even when 1 mg/kg/day has failed to induce a remission [C].*

- *When IgE levels fall appropriately, alternate day doses of oral prednisolone can be tapered by 5 to 10 mg per month to zero over the next 8 to 12 weeks. Repeat chest X-ray after 1-2 months to ensure clearance of radiological changes and again 4-6 monthly to screen for new infiltrates. A sharp rise in IgE heralds a relapse, necessitating an increased dose of prednisolone [C].*

- *The use of the anti-fungal agent itraconazole to treat ABPA is not well established and there are no controlled trials on its use (Elphick & Southern, 2002 [Ia]). However, itraconazole suspension (not capsules) appears to have some effect as a steroid-sparing agent after frequent relapses (Nepomuceno et al, 1999 [III]). Some clinicians would start itraconazole at the same time as prednisolone. Doses between 100 to 200 mg twice-daily have been used (Mannes et al, 1993 [IV]; Denning et al, 1991 [III]). Although there are usually no problems, itraconazole can cause liver dysfunction, and has important drug interactions with antacids and H_2 antagonists, which decrease absorption. Its use can also cause increased systemic levels of cisapride and antihistamines, with risks of ventricular arrhythmia. Serum levels can be measured to ensure adequate absorption but they do not always reflect sputum levels and there is some doubt as to what represents an adequate therapeutic level (Sermel-Gaudelius et al, 2001 [III]) [C].*

- *Nebulised amphotericin has been used with some success in reducing the allergen load and may be of help in recurrent cases (10 mg amphotericin of the preparation for injection 2 to 4 times per day dissolved in water, not saline; 20 ml water is added to each 50 mg vial of amphotericin to achieve a dose of 10 mg in 4 ml to nebulise) [C].*

- *The patient should be advised against 'mucking out' stables and visiting other places where there is rotting vegetation likely to be associated with a high spore count. Hospitals where extensive demolition and building are in progress may also pose a risk [B].*

7.5.3 References

Bargon J, Dauletbaev N, Kohler B, Wolf M, Posselt HG, Wagner TO. Prophylactic antibiotic therapy is associated with an increased prevalence of Aspergillus colonization in adult cystic fibrosis patients. Respir Med 1999; 93:835-838.

Denning, DW, Van Wye JE, Lewiston NJ, Stevens DA. Adjunctive therapy of allergic bronchopulmonary aspergillosis with itraconazole. Chest 1991; 100:813-9.

el-Dahr JM. Fink R, Selden R, Arruda LK, Platts-Mills TA, Heymen PW. Development of immune responses to Aspergillus at an early age in children with cystic fibrosis. Am J Respir Crit Care Med 1994; 150:1513-1518.

Elphick H, Southern K. Antifungal therapies for allergic bronchopulmonary aspergillosis in people with cystic fibrosis (Cochrane Review. In: Cochrane Library, Issue 3, 2002. Oxford: Update Software.

Gilbert J, Littlewood JM. Enteric coated prednisolone in cystic fibrosis. Lancet 1986; ii: 1167-1168.

Mannes GP, van der Heides S, van Aalderen WM, Gerritsen J. Itraconazole and allergic bronchopulmonary aspergillosis in twin brothers with cystic fibrosis. Lancet 1993; 341:492.

Marchant JL, Warner JO, Bush A. Rise in total IgE as an indicator of allergic bronchopulmonary aspergillosis in cystic fibrosis. Thorax 1994; 49:1002-1005.

Nepomuceno IB, Esrig S, Moss RB. Allergic bronchopulmonary aspergillosis in cystic fibrosis: role of atopy and response to itraconazole. Chest 1999; 115:364-370.

Ricketti AJ, Greenburger PA, Patterson R. Serum IgE as an important aid in management of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 1984; 74:68-71.

Sermet-Gaudelus I, Lesne-Hulin A, Lenoir G, Singlas E, Berche P, Hennequin C. Sputum itraconazole concentrations in cystic fibrosis patients. Antimicrob Agents Chemother 2001; 45:1937-1938.

Simmonds EJ, Littlewood JM, Evans EGV. Cystic fibrosis and allergic bronchopulmonary aspergillosis. Arch Dis Child 1990; 65:507-511.

8. MICROBIOLOGICAL APPENDICES

8.1 Culture and identification of major pathogens

Microbiology practice plays a significant role in the management of CF respiratory infection (Shreve et al, 1999 [IV]). It would be impractical to provide dogmatic guidelines for culture and identification of all the major CF pathogens from CF respiratory secretions. However, the following laboratory protocols take account of the idiosyncrasies of CF microbiology (e.g. polymicrobial populations, the presence of multiple colonial morphotypes, differences in antibiotic susceptibility within a single specimen) and may provide useful microbiological information to facilitate early diagnosis and anti-pseudomonal therapy in exacerbations.

- Freshly collected sputum is liquefied by treatment for 15 minutes with an equal volume of Sputalysin (Calbiochem) and intermittent vortexing.

- Using calibrated pipettes and sterile disposable tips, liquefied sputum is diluted 10^2 to 10^4 fold in sterile physiological saline. Volumes (0.1 ml) of each dilution, and of undiluted sputum, are inoculated on to agar culture media and spread evenly with the aid of small sterile glass 'hockey sticks'. Use of appropriate media (selective or enriched) is important and should include the following or appropriate substitutes:

  - *S. aureus*: Blood agar.
  - *H. influenzae*: Chocolate blood agar (CBA) with bacitracin (300 mg/l) or cefsulodin CBA (Smith & Baker, 1997 [III]).
  - *P. aeruginosa*: Difco Pseudomonas Isolation Agar.
  - *S. maltophilia*: Pseudomonas Isolation Agar (Difco) or vancomycin-imipenem-amphotericin B medium (Kerr et al, 1996 [III]).
  - *B. cepacia*: Cepacia Medium (Mast) or Cepacia selective medium (Henry et al, 1997 [III]).

- Plates are incubated aerobically at 37°C with the exception of CBA, which should be incubated in an atmosphere of 5% CO_2. Bacterial growth should be visible within 24 hours but confirmation of mucoidy in *P. aeruginosa* may require 48 hours or longer. In the case of *B. cepacia*, incubation may need to be extended to 72 hours.

- Presumptive identification of *S. aureus*, *H. influenzae* and classical non-mucoid green-pigmented *P. aeruginosa* present few difficulties. However, once *P. aeruginosa* infection is established in patients with CF the colonial morphology may become very atypical and species identification may require the use of a multitest system such as API 20NE. These should also be used for the identification of *S. maltophilia*. Culture, identification and storage of *B. cepacia* can present difficulties. Identification of *B. cepacia* infection requires growth on either of the selective media mentioned above and confirmation by API 20NE or confirmation by a reference laboratory. Details of key laboratory procedures concerning culture, maintenance and identification are discussed elsewhere (Pitt & Govan, 1993 [IV]; Henry et al, 1997 [III]; Coenye et al, 2001 [III]).

8.2 Quantitative microbiology

The value of quantitative culture of CF pathogens in sputum has been long debated. If the

laboratory facilities allow, estimating the number of colony forming units of individual pathogens has several advantages.

● Dilution of the original specimen reduces the likelihood of overgrowth of delicate pathogens – *H. influenzae* in particular – by other organisms, and allows judgement of whether the presence of *H. influenzae* is clinically significant (>10^6 cfu/ml sputum) or merely the result of contamination by commensal strains from the upper airways.

● In conjunction with selective medium, bacterial counts allow assessment of the efficacy of antimicrobial treatment in reducing the bacterial load in the lung. This is most readily observed in the early stages of infection or during the first few treatments with a new antimicrobial.

8.3 Non-cultural techniques

Rapid DNA-based techniques with high sensitivity and accuracy are available for detection of *P. aeruginosa* (McIntosh et al, 1992 [IIb]; Filho et al, 1999 [IIb]) and are presently under development and assessment for use in diagnosis of *B. cepacia* and *S. maltophilia* infections (Whitby et al, 1998 [IIb]). Despite the enthusiasm for the future diagnostic possibilities of these techniques caution should be exercised in respect of their applicability (Vaneechoutte, 1999 [III]).

8.4 Sensitivity testing

The complex nature of CF microbiology is reflected in the long-standing debate on the value of sensitivity testing of CF pathogens. Only relatively recently has the rationale and prophylactic value of early antipseudomonal therapy been accepted and widely practised in the UK and Europe (Littlewood et al, 1985 [IV]; Govan et al, 1987 [IV]; Valerius et al, 1991 [Ib]).

Results of 'routine' sensitivity testing often are not reflected in therapeutic efficacy. An explanation for this discrepancy is that, as colonisation progresses, considerable heterogeneity arises, with different colonial morphotypes of the same strain, and even similar morphotypes exhibiting a range of sensitivity. Thus *in vitro* susceptibility tests based on examination of a single colonial representative may not reflect the true populations of *P. aeruginosa* within the lung. When different colonial morphotypes of the same pathogen are cultured a representative of each morphotype should be tested by the British Society for Antimicrobial Chemotherapy, disc susceptibility test (BSAC Working Party, 2001 [IV]). In a recent study MICs determined by custom-prepared broth microdilution plates (PML Microbiologicals, Portland, Oregon) compared favourably with MICs determined by agar dilution (Saiman et al, 1999 [III]).

8.5 Synergy testing

Synergy testing of antimicrobial combinations is time consuming and, with the exception of troublesome pan-resistant isolates, of doubtful value in the case of isolates from CF pulmonary exacerbations. Moreover clinical interpretation of these *in vitro* results is tenuous in the extreme especially when multiple morphotypes are present. We recommend that such testing should be used only as a last resort in the case of life-threatening intransigent infections.

There is recognised clinical synergy between aminoglycosides and β-lactams (especially penicillins) against *P. aeruginosa*, but clinical evidence of synergy between other combinations of antipseudomonal agents is tenuous or absent. For the occurrence of synergy between antimicrobials against *B. cepacia* **(see Section 7.4)**.

8.6 National Reference Laboratories at Colindale and Edinburgh

The need for reference centres to assist clinicians and microbiological laboratories in the identification, treatment, epidemiology and surveillance of the major CF pathogens is increasingly apparent. Thus, for example, an extensive outbreak of β-lactam resistant *P. aeruginosa* in a large UK Specialist CF Centre was only identified during preparation for a Phase III antibiotic trial (Cheng et al, 1996 [IV]). More recently outbreaks of highly transmissible strains of *P. aeruginosa* have been reported from a number of Specialist CF Centres in the UK (Jones et al, 2001 [III]; McCallum et al, 2001 [III]).

In the case of *B. cepacia* there is a specific need for reference laboratories to confirm the identification of difficult isolates and to identify genomic markers associated with transmissibility and virulence. The US CF Foundation, in association with the University of Michigan and Cornel University, has established a *B. cepacia* Research Laboratory and an Antibiotic Synergy Testing Service to support CF Centres throughout the United States. The Foundation provides support for these facilities and patients and clinical microbiology laboratories are not charged for specimen transport or for the service provided.

In the UK 2 laboratories receive some funding from the Cystic Fibrosis Trust. In addition to local facilities in England and Wales, reference facilities are available through:

Dr. Ty Pitt, The Laboratory of Hospital Infection, Public Health Laboratory Service, 61 Colindale Avenue, London NW9 5HT.

Complementary facilities are also available at:
Professor John Govan, The Cystic Fibrosis Microbiology Laboratory and Strain Repository, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG.

The function of these reference services is to augment and not replace the sputum culture and species identification provided by the diagnostic microbiology laboratories supporting Specialist CF Centres and CF Clinics. The support provided by both laboratories includes advice on specific cases of infection and the following practical services:

● Confirmatory identification of atypical isolates of *P. aeruginosa* and putative isolates presumptively but not reliably identified as *B. cepacia* by the referring laboratory.

● Strain repositories for storage and comparison of *P. aeruginosa* recovered from UK Specialist CF Centres.

● Genomic fingerprinting to identify clusters of similar strains within patient populations. In such situation, consultation is provided to link local and national developments and exchange strains between Colindale and Edinburgh.

● DNA-based analysis using polymerase chain reaction (PCR) amplification of genomic DNA for presence of genomic markers associated with genomovar status and epidemic markers including the cblA gene (Sun et al, 1995 [III]) and the *B. cepacia* epidemic strain marker, BCESM, (Mahenthiralingham et al, 1997 [III]).

In addition, the Cystic Fibrosis Microbiology Laboratory and Strain Repository in Edinburgh would be prepared to:

● Perform antibiotic sensitivity testing by MIC assays to augment routine clinic testing. The

service extends to testing of new antimicrobials against multiresistant isolates. These may be available for clinical use on a named patient compassionate basis.

● Examine an annual sputum specimen from patients with CF chronically infected with *P. aeruginosa* to identify unusual or multiresistant strains at an early stage. These specimens could be conveniently collected at the time of the Annual Review. Specimens for reference laboratories should be sent in accordance with the prevailing postal regulations.

It is normal practice for the results to be sent to both the referring clinical microbiology laboratory and the clinician unless otherwise indicated.

8.7 References

BSAC Working Party. Antimicrobial susceptibility testing. BASC Working Party Report. J Antimicrobiol Chemother 2001; 48 (Suppl S1): 43-57.

Cheng K, Smyth RL, Govan JRW, Doherty C, Winstanley C, Denning C, et al. Spread of β-lactam resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. Lancet 1996; 348:639-642.

Coenye T, Vandamme P, Govan JRW, LiPuma JJ. Taxonomy and identification of *Burkholderia cepacia* complex. J Clin Microbiol 2001; 39:3427-3436.

Filho LVF da S, Levi JE, Bento CNO, Ramos SI, Rozov T. PCR identification of *Pseudomonas aeruginosa* and direct detection in clinical samples from cystic fibrosis patients. J Med Microbiol 1999; 48:357-361.

Govan JRW, Doherty C, Glass S. Rational parameters for antibiotic therapy in patients with cystic fibrosis. Infection 1987; 15:300-307.

Henry DA, Campbell ME, LiPuma JJ, Speert DP. Identification of *Burkholderia cepacia* isolates from patients with cystic fibrosis and use of a simple new selective medium. J Clin Microbiol 1997; 35:614-619.

Jones AM, Govan JRW, Doherty CJ, Dodd ME, Isalska BJ, Stanbridge TN, et al. Spread of a multiresistant strain of *Pseudomonas aeruginosa* in an adult cystic fibrosis clinic. Lancet 2001; 358:557-558.

Kerr KG, Denton M, Todd NJ, Corps CM, Kumari P, Hawkey PM. A novel selective culture medium for the isolation of *Stenotrophomonas maltophilia*. Eur J Clin Microbiol Infect Dis 1996; 15:607-610.

Littlewood J, Miller MG, Ghoneim AG, Ramsden CH. Nebulised colomycin for early pseudomonas colonisation in cystic fibrosis. Lancet 1985; i: 865.

McCallum SJ, Corkill J, Gallagher M, Ledson MJ, Hart CA, Walshaw MJ. Superinfection with a transmissible strain of *Pseudomonas aeruginosa* in adults with cystic fibrosis chronically colonised by *P. aeruginosa*. Lancet 2001; 358:558-560.

McIntosh I, Govan JRW, Brock DJH. Detection of *Pseudomonas aeruginosa* from cystic fibrosis patients by polymerase chain reaction. Mol Cell Probes 1992; 6:299-304.

Mahenthiralingam E, Simpson DA, Speert DP. Identification and characterization of a novel DNA marker associated with epidemic *Burkholderia cepacia* strains recovered from patients with cystic fibrosis. J Clin Microbiol 1997; 35:808-816.

Pitt TL, Govan JRW. *Pseudomonas cepacia* and cystic fibrosis. PHLS Microbiol Dig 1993; 10:69-72.

Saiman L, Burns JL, Whittier S, Krzewinsky J, Mundil SA, Jones RN. Evaluation of reference dilution test methods for antimicrobial susceptibility testing of *Pseudomonas aeruginosa* strains isolated from patients with cystic fibrosis. J Clin Microbiol 1999; 37:2987-2991.

Shreve MR, Butler S, Kaplowitz HJ, Rabin HR, Stokes D, Light M. Impact of microbiology practice on cumulative prevalence of respiratory tract bacteria in patients with cystic fibrosis. J Clin Microbiol 1999; 37:753-757.

Smith A, Baker M. Cefsulodin chocolate blood agar: a selective medium for the recovery of *Haemophilus influenzae* form the respiratory secretions of patients with cystic fibrosis. J Med Microbiol 1997; 4:883-885.

Sun L, Jiang RZ, Steinbach S, Holmes A, Campanelli C, Forstner J, et al. The emergence of a highly transmissible lineage of cbl+ *Pseudomonas (Burkholderia) cepacia* causing CF centre epidemics in North America and Britain. Nature Med 1995; 1:661-666.

Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. Lancet 1991; 338:725-726.

Vaneechoutte M. A plea for caution with regard to applicability of PCR for direct detection. J Clin Microbiol 1999; 37:3081.

Whitby PW, Dick HLN, Campbell III PW, Tullis DE, Matlow A, Stull T. Comparison of culture and PCR for detection of *Burkholderia cepacia* in sputum samples of patients with cystic fibrosis. J Clin Microbiol 1998; 36:1642-1645.

9. 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 Ed. Hill CM. 1998.

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.

Please check carefully whether the dose/kg stated is the total per 24 hours or for each individual dose.

9.1 Continuous anti-staphylococcal therapy

Flucloxacillin	**Child: 50 to 100 mg/kg/day PO.**
	Conveniently given in a bd dosage but ideally qds.
	Adults: Maximum 1 g qds.
Available preparations:	125 mg/5 ml and 250 mg/5 ml suspensions.
	250 and 500 mg capsules.
Administration:	Give 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.
Note:	Low doses should be given initially, for example 250 mg/day, and these should be adjusted upwards if staphylococci continue to be isolated and despite good adherence.

Cephradine	**25 to 50 mg/kg/day in 2-4 doses (max. 4 g daily)**
	or for CF: birth-1 yr 500 mg bd,
	1-7 yrs 1 g bd,
	7-12 yrs 2 g bd,
	>12 yrs and adults (max. 2 g bd).
Available as:	250 mg/5 ml suspension, 250 mg 500 mg capsules.
Administration:	After food.
Side effects:	Gastrointestinal upset, hypersensitivity reactions to penicillins.

9.2 Treatment of asymptomatic *Staphylococcus aureus* isolates or minor exacerbations

Flucloxacillin	**Child: 50 to 100 mg/kg/day in 3-4 divided doses.**
	Adult: 50 to 100 mg/kg/day. Maximum in 1 g qds.

Erythromycin	**Child: 50 mg/kg/day in 2 to 4 divided doses.**
	Or under 2 yrs 250 mg,
	2-8 yrs 500 mg,
	over 8 yrs 1 g all given bd.
	Adult: 1 g twice-daily.
Available:	125 mg/5ml, 250 mg/5 ml, 500 mg/5 ml, 250 mg and 500 mg tablets and capsules.
Administration:	With or after meals.

Side effects:	Gastrointestinal disturbance, allergic reactions.
Caution:	Interacts with a variety of other drugs including cisapride, theophylline and cimetidine.
Note:	Has been used as a long-term anti-staphylococcal drug for many years by some experienced clinicians.

Azithromycin	**Child: 10 mg/kg/day od PO for 3 days.** **Repeat course 1 week later. Repeat again as necessary.** **Adult: 500 mg od PO for three days.**
Available preparations:	200 mg/5 ml suspension, 250 mg capsules, 500 mg tablets.
Administration:	Give on an empty stomach.
Side effects:	Gastrointestinal disturbances, allergic reactions and drug interactions, but less than with erythromycin.
Note:	**Resistance can occur with repeated courses.** **Also used as an anti-inflammatory in children over 8 yrs** **(see Section 4.1)** **<40 kg 250 mg daily.** **>40 kg 500 mg daily.**

Sodium Fusidate	**Child: <5 yrs 250 mg (5 ml) tds.** **5-12 yrs 500 mg (10 ml) tds.** **12 yrs and over 750 mg fusidic acid (15 ml) tds.** **or 500 mg sodium fusidate (2 tabs) tds.** **Adult: 750 mg tds PO.**
Available preparations:	250 mg/5 ml fusidic acid suspension, (equivalent to 175 mg sodium fusidate). 250 mg sodium fusidate tablets (equivalent to 240 mg fusidic acid).
Administration:	Traditionally used in combination with another antibiotic, e.g. flucloxacillin, to prevent resistance although scientific basis is doubtful.
Side effects:	Gastrointestinal disturbances, skin rashes, jaundice. Avoid in liver disease.

Clindamycin	**Child: 20-30 mg/kg in 3 or 4 divided doses PO.** **Adult: Maximum 600 mg qds PO.**
Available preparations:	75 mg/5 ml suspension, 75 mg and 150 mg capsules.
Administration:	Absorption is not affected by food.
Side effects:	Nausea and vomiting, diarrhoea, pseudomembranous colitis (if diarrhoea occurs advise to discontinue the drug and obtain immediate medical advice), blood dyscrasias, dermatitis and hypersensitivity reactions. Monitor liver and renal function if therapy is prolonged.

9.3 Treatment of more severe exacerbations caused by *Staphylococcus aureus*

Flucloxacillin	**Child: 100 mg/kg/day in 4 doses 6 hourly IV.** **Adult: 1 g-2 g 6 hourly IV (max. 8 g daily).**
Available preparations:	250 mg, 500 mg and 1 g vials.
Administration:	By slow intravenous injection over 3-4 minutes.
Side effects:	See above. Reduce dose in renal impairment.

Aminoglycosides	See under treatment of *P. aeruginosa* (**Section 9.8.5**).

Note: It is advisable to reserve vancomycin, teicoplanin and rifampicin for MRSA infection or serious *S. aureus* infections that do not respond to other anti-staphylococcal drugs.

Vancomycin	**Child: 45 mg/kg/day in 3 or 4 divided doses IV.**
	Adult: 1 g bd IV.
	These are starting doses – amend according to levels achieved.
Available preparations:	250 mg and 500 mg vials.
Administration:	Intravenous infusion. Must be given slowly over a minimum of 1 hour or at 10 mg/min.
Side effects:	Infusion related events: 'red man' syndrome if infusion given too quickly, nephrotoxicity, ototoxicity, reversible neutropenia and thrombocytopenia.
Note:	Reduce dosage or avoid in renal impairment. Monitor levels after 3rd dose – trough levels of 5-10 mg/l are acceptable although a trough up to 15 mg/l may be preferred in severe infections and peak at 1 hr after completion of infusion of 18-25 mg/l. (Always check local policy.)

Rifampicin	**Child: 10-20 mg/kg od PO.**
	Adult: 600-1200 mg in 2 to 4 divided doses.
Available preparations:	Syrup 100 mg/5 ml.
	Capsules 150 mg and 300 mg.
Administration:	Use in combination with another appropriate antibiotic (e.g. fusidic acid) to prevent resistance. Give on an empty stomach.
Side effects:	Flushing and itching, gastrointestinal reactions, hepatitis, thrombocytopenia, reddish discolouration of urine, sputum and tears (soft contact lenses may be permanently stained). Use with extreme caution in liver impairment, monitor liver function in prolonged treatment. Rifampicin induces liver enzymes and therefore the elimination of other drugs (e.g. oral contraceptives) may be increased.

Teicoplanin	**Child: Severe infections 10 mg/kg every 12 hours for 3 doses and then 10 mg/kg daily IV as single dose.**
	Adults: 400 mg IV every twelve hours for 3 doses then 400 mg IV daily.
Available preparations:	Vials 200 mg and 400 mg.
Administration:	By slow IV injection.
Side effects:	Local reactions and hypersensitivity reactions. Caution if there has been hypersensitivity to vancomycin.
	See SPC for details.

Linezolid	**Child: <5 yrs 30 mg/kg/day in 3 divided doses.**
	>5 yrs 20 mg/kg/day in 2 divided doses.
	Adult: 600 mg twice-daily.
Available preparations:	600 mg tablets and IV infusions,
	Liquid 100 mg/5 ml.

Administrations:	Oral or intravenous.
Side effects:	Many side effects including myelosuppression.
	Requires careful monitoring.
Note:	A new preparation not licensed in children.
	Discuss with pharmacist and manufacturer **(see Section 7.1.2).**

9.4 Treatment for asymptomatic *Haemophilus influenzae* carriage or mild exacerbations

Amoxycillin	**Child: 50-100 mg/kg/day in 3 divided doses.**
	Or under 1 yr 125 mg tds,
	1-7 yrs 250 mg tds,
	>7 yrs 500 mg tds.
	Adult: 500 mg tds.
Available preparations:	125 mg/1.25 ml, 125 mg/5 ml, 250 mg/5 ml syrup or suspension, 250 mg and 500 mg capsules.
Administration:	Absorption not affected by food.
Side effects:	Nausea, diarrhoea and rashes.
Note:	Up to 20% of *H. influenzae* isolates are now resistant to amoxycillin – important to check sensitivity. Most have β-lactamase and will be susceptible to amoxycillin/clavulanate which overcomes these.

Cefaclor	**Child: 1 mth-1 yr 125 mg tds, 1-7 yrs 250 mg tds,**
	>7 yrs 500 mg tds PO.
	Adult: 500 mg tds PO.
Available preparations:	125 mg/5 ml, 250 mg/5 ml suspension, 250 mg and 500 mg capsules, (375 mg MR tablets for bd dosage).
Administration:	Absorption is not affected by food.
Side effects:	Diarrhoea, nausea and vomiting, headache, allergic reactions and blood dyscrasias.

Cefixime	**Child: 6 mths-1 yr 75 mg od,**
	1-4 yrs 100 mg od,
	5-12 yrs 200 mg od,
	>12 yrs 400 mg od PO.
	Adult: 400 mg od PO.
Available preparations:	100 mg/5 ml suspension. 200 mg tablets.
Administration:	Absorption not affected by food.
Side effects:	Similar to those of cefaclor.
Note:	Reserved for resistant *H. influenzae* infections.

Azithromycin as for *Staphylococcus aureus* **(see Section 9.2)**

9.5 Treatment of severe exacerbation of *Haemophilus influenzae* infection

Cefuroxime	**Child: 200 mg /kg/day 6 hourly IV.**
	Adult: 750 mg-1.5 g 6 hourly IV.
Available preparations:	250 mg, 750 mg and 1.5 g vials.
Administration:	By slow intravenous injection.
Side effects:	See cefaclor **(see Section 9.4)**. Reduce dose in renal impairment.

Cefotaxime	Child: 150 mg/kg/day in 2 to 4 doses IV (max. 200 mg/kg/day).
	Adult: 2 g tds IV (max. 12 g daily).
Available Preparations:	500 mg, 1 g, 2 g vials.
Administration:	Slow IV injection.
Side effects:	See cefaclor **(see Section 9.4)**.
Note:	Less active against *S. aureus* than cefuroxime.

9.6 Treatment of atypical infection e.g. Mycoplasma

Erythromycin	Details in Section 9.2.
Clarithromycin	**Child: <8 kg 7.5 mg/kg bd.**
	1-2 yrs 62.5 mg bd.
	3-6 yrs 125 mg bd.
	7-9 yrs 187.5 mg bd.
	>10 yrs 250 mg bd.
	IV dose 15 mg/kg/day in 2 divided doses.
	Adults: 250 mg bd (max. 500 mg bd).
	IV dose 15 mg/kg/day (max. 500 mg bd).
Available preparations:	125 mg/5 ml, tablets 250 mg and 500 mg.
	Also IV preparation 500 mg per vial.
Administration:	Oral with food. IV dilute to 2 mg/ml and give over 1 hr.
Side effects:	See erythromycin. A variety of drug interactions. See current SPC .
	Important to see data sheet before using.
Azithromycin	Details in Section 9.2.

9.7 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 (**see Section 4.4** for details).

Ciprofloxacin	**Child: <5 yrs PO 10-30 mg/kg/day in 2 divided doses.**
	IV 8-16 mg/kg/day in 2 divided doses.
	5-17 yrs PO 40 mg/kg/day in 2 divided doses
	(max. 1500 mg daily).
	IV 30 mg/kg/day in 2 divided doses.
	Adult: PO 750-1000 mg bd.
	IV 400 mg bd.
Available preparations:	100 mg, 250 mg, 500 mg, 750 mg tablets.
	Suspension 250 mg/5 ml.
	IV preparations are 100 mg, 200 mg and 400 mg.
Administration:	Avoid alcohol and exposure to strong sunlight.
Side effects:	Side effects include nausea, vomiting, joint pain, abdominal pain, headache, rash, dizziness, pruritus, hepatitis and jaundice. Nausea commonly resolves after with lower doses. A photosensitive skin erythema is relatively common. Use with caution in epileptic patients. Reduce dose in severe renal impairment.
Note:	Ciprofloxacin is now licensed for acute pulmonary exacerbations associated with *P. aeruginosa* in patients with CF aged 5-17 years

and also for non-CF patients without a lower age limit. Although there were initial concerns about arthropathy in weight bearing joints in young animals, the drug has been widely used in children with CF to treat *P. aeruginosa* infections with good effect and without serious side effects.

Antimicrobial sensitivity: While ciprofloxacin does have activity against gram-positive infections, there is a high incidence of resistance in *S. aureus* after repeated dosing.

9.8 Treatment of early *Pseudomonas aeruginosa* infections not cleared by ciprofloxacin and colistin and of moderate to severe exacerbations of *Pseudomonas aeruginosa* infection

Please **see Section 6** for full discussion of intravenous antibiotic therapy and **Section 6.6** for choice of antibiotics.

First-line treatment

An anti-pseudomonal penicillin or ceftazidime in combination with an aminoglycoside is recommended. Combination therapy minimises the risk of selecting resistant organisms and produces useful synergistic effects. A combination of intravenous tobramycin and ceftazidime is popular and effective if the organisms are sensitive.

9.8.1 Anti-pseudomonal penicillins

Ureidopenicillins (piperacillin) have greater antimicrobial activity against *P. aeruginosa* than the carboxypenicillins (carbenicillin or ticarcillin). Anti-pseudomonal penicillins also have activity against most *H. influenzae* but not *S. aureus*. The addition of a β-lactamase inhibitor tazobactam to piperacillin (Tazocin) and clavulanic acid to ticarcillin (Timentin) confer activity against *S. aureus*. Azlocillin ceased to be available in 1999. Piperacillin is only available combined with tazobactam.

Piperacillin/Tazobactam	**Child: 90 mg /kg/every 6-8 hrs IV.**
	Adult: 2.25 g to 4.5 g every 6-8 hrs IV.
Available preparations:	2.25 g (piperacillin 2 g and tazobactam 250 mg) 4.5 g (piperacillin 4 g and tazobactam 500 mg) vials.
Administration:	Slow IV injection.
Side effects:	Hypersensitivity reactions, gastrointestinal reactions, blood dyscrasias.
Note:	**One adult CF Centre uses 4.5 g every 6 hrs.**
	Licensed for children over 2 yrs.

Ticarcillin/Clavulanic acid	**Child: 330-400 mg/kg/day IV in 4 divided doses.**
	Adult: 3.2 g 6 hourly IV (max. 24 g/day.)
Available preparations:	1.6 g (ticarcillin 1.5 g and clavulanic acid 100 mg).
	3.2 g (ticarcillin 3 g and clavulanic acid 200 mg) vials.
Administration:	IV infusion over 30-40 minutes.
Side effects:	Gastrointestinal upset, rash, hepatitis and cholestatic jaundice.
Note:	Reduce dosage in renal impairment. May be useful in *S. maltophilia* infection.

9.8.2 Third generation cephalosporins

These should always be administered with another antibiotic, usually an aminoglycoside, so as to reduce the emergence of resistant organisms and improves efficacy. They have little activity against *Staphylococcus aureus*.

Ceftazidime	**Child: 150 to 200 mg/kg/day in 3 divided doses IV.** **Can be given in 2 doses (max. 6 g/day).** **Adult: 2 g to 3 g tds IV (max. 9 g/day).**
Available preparations:	250 mg, 500 mg, 1 g, 2 g and 3 g vials.
Administration:	Slow IV injection.
Side effects:	Rash, hypersensitivity reactions, diarrhoea, nausea and vomiting, headache and bad taste.
Note:	Reduce dose in renal impairment. **One adult Specialist CF Centre uses up to 6 g every 6 hrs in *B. cepacia* infections.**

Second-line treatments

9.8.3 Other β-lactam antibiotics

These drugs can be used as second-line agents if hypersensitivity reactions have occurred following anti-pseudomonal penicillins or cephalosporins provided the organisms are sensitive. Useful in patients allergic to ceftazidime.

Aztreonam	**Child: 200 to 250 mg/kg/day in 4 divided doses IV (max. 8 g in 24 hr).** **Adult: 2.0 g 6 hourly.**
Available preparations:	500 mg, 1 g and 2 g vials.
Administration:	Slow IV injection.
Side effects:	Rash, blood dyscrasias diarrhoea, nausea, vomiting, jaundice and hepatitis.
Note:	Reduce dose in moderate to severe renal impairment. Can be given as a tds regimen – 200-250 mg/kg/day in 3 divided doses (equates to 80 mg /kg/dose) is used in one CF Centre without problems.
Antimicrobial sensitivity:	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/Cilastin	**Child: 90 mg/kg/day in 4 divided doses IV (max. 4 g in 24 hrs).** **Adult: 1 g tds IV (max. 4 g in 24 hrs).**
Preparations available:	250 mg imipenem with 250 mg cilastin. 500 mg imipenem with 500 mg cilastin.
Administration:	500 mg or less, infuse over 30 minutes, >500 mg, infuse over 60 minutes.
Side effects:	Rash, nausea, and vomiting (may be helped by reducing infusion rate), blood dyscrasias, confusion, dizziness and seizures.
Note:	Use with caution in patients with central nervous system disorders and reduce dosage or avoid in renal impairment.

Resistance commonly selected in *P. aeruginosa* (only) when used as monotherapy.

As a β-lactam inducer it should never be prescribed with another β-lactam antibiotic e.g. piperacillin, ceftazidime, aztreonam.

Antimicrobial sensitivity:	Active against *S. aureus* and *H. influenzae* as well as *P. aeruginosa*.

Meropenem	**Child: 120 mg/kg/day in 3 divided doses IV (max. 2 g tds).**
	Adult: 1 g to 2 g tds IV.
Available preparations:	250 mg, 500 mg and 1 g vials.
Administration:	Slow IV injection.
Side effects:	Skin reactions, gastrointestinal reactions, blood dyscrasias and headache.
Antimicrobial sensitivity:	As for imipenem. Useful in *B. cepacia* infections.

9.8.4 Polymyxins

Indicated for IV treatment of multiresistant organisms where there are no available alternatives. Active against most gram-negative organisms but not *B. cepacia* and not against any gram-positive species. The majority of *P. aeruginosa* are sensitive; resistance has only very rarely been reported. In practice a *P. aeruginosa* reported to be resistant to colistin often turns out to be some other organism, such as *B. cepacia*.

Colistin	**Child: 50,000 to 75,000 units /kg/day IV in 3 divided doses.**
	Adult: 2,000,000 units IV 8-hourly
Available preparations:	500,000 and 1,000,000 unit vials.
Administration:	Slow IV infusion.
Side effects:	Sensory disturbances, vasomotor instability, visual disturbance, confusion and neurotoxiticy.
Note:	Reduce dosage in renal impairment and when used in combination with nephrotoxic drugs. Monitor renal function.
Antimicrobial sensitivity:	The majority of *P. aeruginosa* are sensitive. Now frequently used in some units where resistance to other drugs is a problem.

9.8.5 Aminoglycosides

These are used in combination with other treatments **(see Sections 9.8.1 and 9.8.2)** and have a synergistic effect with β-lactams. Higher doses are required in people with CF owing to increased plasma clearance. Consider hearing tests for those receiving repeated dosages. Tobramycin is recommended, as it is more active against *P. aeruginosa* than gentamicin. **(Please see Sections 6.6 to 6.8.)**

Tobramycin	**Child: 10 mg/kg/day in 3 divided doses IV.**
(also gentamicin)	**Adult: 9-12 mg/kg/day in 3 divided doses IV.**
Available Preparations:	Tobramycin 20, 40, 80 mg vials.
	Gentamicin 20, 80 mg ampoules.
Administration:	IV injection. Do not mix with other antibiotics in the same syringe.
Side effects:	Nephrotoxicity and ototoxicity.
Note:	Ensure adequate hydration and normal renal function at the start of therapy. Monitor blood levels after the third 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. Reduce dosage in renal impairment.

Antimicrobial sensitivity:	Also active against *S. aureus* and *H. influenzae*.
Note:	Some Specialist CF Centres are now using once-daily treatment **(see Section 6.8)**. A multicentre UK trial of this practice started in 1999 and is due for completion in 2002. (Trial co-ordinated by Dr. Alan Smyth, City Hospital, Nottingham who can provide further up-to-date information.)
Amikacin	**Child: 30 mg/kg/day in 3 divided doses IV.** **Adult: 15 mg/kg/day in 2 doses IV.**
Available preparations:	100 mg and 500 mg in 2 ml.
Note:	Aim for trough level of <10 mg/l. Peak should not exceed 25 to 30 mg/l at 1 hr. Discuss with local microbiology laboratory.

9.9 Nebulised anti-pseudomonal antibiotics

There are currently two preparations licensed for the treatment of *P. aeruginosa* in cystic fibrosis, colistin (Colomycin) and preservative free tobramycin (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 (**see Sections 4.4 and 5.2)**. Nebulised colistin is widely used as long-term treatment for patients chronically infected with *P. aeruginosa* (**see Section 5)**.

Colistin	**Child: <2 yrs 1 mega unit bd.** **>2yrs and Adult: 2 mega units bd. (see *Note below)**
Available preparations:	500,000 and 1,000,000 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.
Note:	Give first dose in hospital and measure lung function before and after dose. ***Some CF Centres recommend 1 mega unit bd. for children <10 yrs; others use 2 mega units bd. >2 yrs, as recommended above, without problems.**
Tobramycin (Preservative-free TOBI)	**Child >6 yrs and Adults: 300 mg bd. Alternating 28 days on and 28 days off.**
Available preparations:	300 mg in 5 ml preservative-free solution.
Side effects:	Voice alteration, local effects, and tinnitus.
Notes:	Alternative nebulised suppressive treatment for patients chronically infected with *P. aeruginosa*. Give first dose in hospital and measure lung function before and after dose. Tobramycin nebuliser solution is licensed for use with the PARI LC Plus nebuliser (provided/ supplied by Chiron) for long-term management of chronic pulmonary infection due to *P. aeruginosa* in patients with CF aged 6 years and older.

Tobramycin (and gentamicin) (Intravenous preparations)	**Child: <5 yrs 40 mg bd. nebulised.** **5-10 yrs 80 mg bd. nebulised.** **>10 yrs 160 mg bd. nebulised.** **Adult: 160 mg bd. nebulised.**
Available preparations:	40 and 80 mg vials. Use phenol-free formulations.
Administration:	Dilute to 4 ml with 0.9% sodium chloride.
Side effects:	Local effects. Occasional bronchospasm.
Note:	Give the first dose in hospital and measure respiratory function before and after dosage.

9.10 Drugs used in the treatment of chronic *Burkholderia cepacia* infections

Extended sensitivity testing may usefully identify oral antibiotics that can be used to treat infections caused by this organism – some are listed below. 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. It is also suggested that all isolates should be sent by the local laboratory to either the Edinburgh Cystic Fibrosis Microbiology Laboratory and Repository (Professor John Govan Tel: 0131 650 3164) or the Laboratory of Hospital Infection, Central Public Health Laboratory, London (Dr. Ty Pitt Tel: 020 8200 4400). Further details available from the Cystic Fibrosis Trust Headquarters Tel: 020 8464 7211 .

Chloramphenicol	**Child: 50-75 mg/kg/day in 4 divided doses PO.** **Adult: 50-75 mg/kg/day in 4 divided doses PO.** **Max. dose 4 g in 24 hrs.**
Available preparations:	250 mg capsules.
Administration:	Absorption not affected by food.
Side effects:	Blood disorders including aplastic anaemia. Monitor blood counts before and during treatment. Also gastrointestinal disturbances, peripheral and optic neuritis.
Antimicrobial spectrum:	Also active against most *H. influenzae* and *S. aureus*.

Co-trimoxazole	**Child: 6 wks-6 mths 120 mg bd. PO.** **6 mths-5 yrs 240 mg bd. PO.** **6 yrs-12 yrs 480 mg bd. PO.** **Adult: 960 mg bd.**
Available preparations:	240 and 480 mg/5 ml syrup and suspension, 480 mg and 960 mg tablets.
Administration:	Absorption not affected by food.
Side effects:	Gastrointestinal disorders, rash (discontinue immediately) blood disorders (discontinue immediately), jaundice. Stevens Johnson syndrome.
Antimicrobial spectrum:	Also active against *S. aureus* and *H. influenzae*.
Notes:	Also useful in *S. maltophilia* infections **(see Section 7.2).**

Doxycycline	**Child: contraindicated under 12 yrs.** **>12 yrs 100-200 mg once a day PO.** **Adult: 200 mg od PO.**
Available preparations:	50 and 100 mg capsules 100 mg dispersible tablets.
Administration:	Swallow whole with plenty of water while sitting or standing.
Side effects:	Gastrointestinal disorders, erythema (discontinue treatment), headache and visual disturbances, hepatotoxicity.
Antimicrobial spectrum:	Also active against most *H. influenzae* and some *S. aureus*.

9.11 Treatment of more severe *Burkholderia cepacia* infection

Ceftazidime	Details in Section 9.8.2.
Meropenem	Details in Section 9.8.3.
Imipenem	Details in Section 9.8.3.

For combinations **see Section 7.4**

9.12 Use of nebulised antimicrobials in chronic *Burkholderia cepacia* infection

Ceftazidime	**Child: 1 g bd.**
	Adult: 1 g bd.
Available preparations:	**Details in Section 9.8.2**
Administration:	Dissolve in 3 ml water for injection.
Side effects:	Sensitivity reactions. Local effects.
Taurolidine	**Adult: 4 ml of 2% solution bd.**
	See Section 5.6.

10. ANTIBIOTIC-RELATED ALLERGIES AND DESENSITISATION

The ideal choice for intravenous therapy in respiratory exacerbations comprises a combination of 2 antibiotics to which the pseudomonas isolates are sensitive and which have synergistic activity i.e. a β-lactam plus an aminoglycoside.

However, 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.

10.1 Extent of the problem

Hypersensitivity reactions are reported with most of the antibiotics in regular use for patients with CF including aminoglycosides (Schretlen-Doherty & Troutman, 1995 [IV]), semisynthetic penicillins (Moss et al, 1984 [IV]), β-lactams (Koch et al, 1991 [IV]) and quinolones (Lantner, 1995 [IV]). 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 (Koch et al, 1991 [IV]). 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 (Wills et al, 1998 [IV]). Seventy-one of 196 (36%) adults with CF experienced one or more antibiotic hypersensitivity reaction (Etherington et al, 1998 [IV]).

10.2 Desensitisation

The idea of using a desensitisation method to prevent recurrence of allergic reaction in patients with CF is well established (Moss et al, 1984 [IV]; Ghosal et al, 1997 [IV]). One 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 (Etherington et al, 1998 [IV]).

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.

Recommendations
Example of a desensitisation regimen [C]

- *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 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 [C].*

- *Adrenaline, hydrocortisone and an antihistamine should be readily available and the appropriate doses for the patient known before starting the procedure [C].*

- *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 (Schretlen-Doherty & Troutman, 1995 [IV]). Other reports of desensitisation include ciprofloxacin (Lantner, 1995 [IV]) and patients with multiple allergic reactions to both β-lactams and aminoglycosides (Earl & Sullivan, 1987 [IV]).

10.3 References

Earl HS, Sullivan TJ. Acute desensitisation of a patient with cystic fibrosis to both beta-lactam and aminoglycoside antibiotics. J Allergy Clin Immunol 1987; 79:477-483.

Etherington C, Whitehead A, Conway SP, Bradbury H. Incidence of antibiotic related allergies in an adult cystic fibrosis unit and the success rate of a desensitisation regimen. Pediatr Pulmonol 1998; Suppl 17; 324. Abstract 427.

Ghosal S, Taylor CJ. Intravenous desensitisation to ceftazidime in cystic fibrosis patients. J Antimicrob Chemother 1997; 39:556-557.

Koch C, Hjelt K, Pedersen SS, Jensen ET, Jensen T, Lanng S, et al. Retrospective clinical study of hypersensitivity reactions to aztreonam and six other beta-lactam antibiotics in cystic fibrosis patients receiving multiple treatment courses. Rev Infect Dis 1991; 13(Suppl 7):S 608-611.

Lantner RR. Ciprofloxacin desensitisation in a patient with cystic fibrosis. J Allergy Clin Immunol 1995; 96:1001-1002.

Moss RB, Babin S, Yao-Pi H. Allergy to semi-synthetic penicillins in cystic fibrosis. J Pediatr 1984; 104:460-466.

Schretlen-Doherty JS, Troutman WG. Tobramycin induced hypersensitivity reaction. Ann Pharmacother 1995; 29:704-706.

Wills R, Henry RL, Francis JL. Antibiotic hypersensitivity reactions in cystic fibrosis. J Paediatr Child Health 1998; 34:325-329.

Notes