Cystic fibrosis papers of the year 2009

Ian M Balfour-Lynn

Department of Paediatric Respiratory Medicine, Royal Brompton & Harefield NHS Foundation Trust, Sydney Street, London SW3 6NP, UK

E-mail: i.balfourlynn@ic.ac.uk

DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
IMB-L

Contributorship
IMB-L is the sole contributor

Acknowledgements
None

Introduction

The literature search was conducted using PubMed (www.ncbi.nlm.nih.gov/sites/entrez), entering the search term 'cystic fibrosis', for the period 1 November 2008 to 15 October 2009. There were 1525 papers identified, and when limits were set for 'clinical trial' and 'randomized controlled trial' this left 40 papers. The papers selected for this review are a personal choice of studies with important or interesting clinical messages.

Case controlled study – CF liver disease

Bartlett JR, Friedman KJ, Ling SC, *et al*.; Gene Modifier Study Group. Genetic modifiers of liver disease in cystic fibrosis. *JAMA* 2009;**302**:1076–83

What is already known?

- Only 3–5% of patients with CF develop severe liver disease (CFLD) resulting in cirrhosis and portal hypertension (PH).
- Liver disease is due to loss of CFTR function on the apical membrane of cholangiocytes resulting in poor flow of bile. This results in inflammation leading to cholangitis and fibrosis in focal portal tracts.
- Genetic polymorphisms are functional variants in genes which may modify disease severity.

Methods

- Two-stage case-controlled study.
- Sixty-three centres in the US, 32 in Canada, 18 outside North America – 34 authors!
- CFLD defined as cirrhosis confirmed by imaging showing parenchymal changes with portal hypertension in anyone aged 2 years or older.
- Controls aged 15 years or above to exclude occult liver disease.
- Stage 1: 123 patients with CFLD *vs*. 843 CF with no liver disease.
- Genotyping 9 polymorphisms in five genes: α_1-Antitrypsin (SERPINA1), angiotensin converting enzyme (ACE), glutathione S-transferase (GSTP1), mannose-binding lectin 2 (MBL2), transforming growth factor β1 (TGFB1).
- Stage 2: different population of 136 patients with CFLD *vs*. 1088 CF with no liver disease studied for SERPINA1 Z allele and TGFB1 codon 10 genotypes.

Results

- Mean age of CFLD diagnosis 10.6 (SD 5.4) years; 90% diagnosed by 20 years.
- Liver biochemistry poorly predictive of severe CFLD and portal hypertension; thrombocytopaenia was common in PH.
- Stage 1 found CFLD associated with SERPINA1 Z allele and TGFB1 codon 10.
- Stage 2 replication study found CFLD associated with SERPINA1 Z allele only.
- Combining the two by logistic regression (adjusted for gender, ethnicity and CFTR genotype) found CFLD associated with SERPINA1 Z allele with odds ratio 5.0 (95% CI 2.9–8.9, $p=1.5 \times 10^{-8}$), i.e. patients with the Z allele have a five-fold greater risk of developing severe liver disease.
- The discussion suggested that in the presence of a single copy of SERPINA1 Z allele, the misfolded SERPINA1 protein accumulates in hepatocytes adjoining fibrosed portal tracts.

This augments the inflammatory stimulation of hepatic stellate cells, which migrate and proliferate in the bile duct regions in a profibrogenic manner.

Critique

- This is a good example of how to conduct a proper polymorphism study – rigorous definition of the disease state (CFLD); methods to exclude occult disease in controls; large number of subjects; two-stage protocol with a replication study in a different population; international collaboration.
- SERPINA1 Z allele is present in 1.2% normal population (*n*=85,000) and 1.14% CF controls (without CFLD). Only 2.2% CF population are carriers of this polymorphism but the odds ratio for CFLD (of 5) is high.
- Should we look for the polymorphism in newborn screened CF children? It might be useful if we could prevent onset of CFLD, perhaps starting ursodeoxycholic acid at that stage but this is unproven.
- Young children should be screened for liver disease early but not by blood tests.

Case-controlled study – intermediate sweat chloride levels

Goubau C, Wilschanski M, Skalická V, *et al*. Phenotypic characterisation of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis. *Thorax* 2009;**64**:683–91

What is already known?

- Patients with intermediate sweat chloride values of 30–60 mmol/L are said to have CFTR dysfunction, if they have two gene mutations identified on extensive mutation analysis; or an abnormal nasal potential difference (NPD).

Methods

- Thirteen centres from 10 countries provided data.
- Phenotypic comparisons were made in four groups:
  - 'CF unlikely' – intermediate sweat Cl^- (30–60 mmol/L) only, with no further evidence of CFTR dysfunction, *n*=46.
  - CFTR dysfunction (sweat Cl^- 30–60 mmol/L plus two genes or abnormal NPD), *n*=59.
  - Classic CF with pancreatic sufficiency, *n*=103.
  - Classic CF with pancreatic insufficiency, *n*=62.

Results

- CFTR dysfunction group classified by two CFTR mutations (52%), or one mutation and abnormal NPD (24%), or abnormal NPD alone (24%).
- In the CF unlikely group, 87% had no mutation identified.
- CFTR dysfunction group had more frequent lower respiratory tract infections ($p<0.01$), more isolation of CF pathogens – *Pseudomonas aeruginosa* and *Staphylococcus aureus* ($p<0.001$), and more clubbing ($p=0.001$) than the 'CF unlikely' group.
- CFTR dysfunction group had less frequent respiratory tract infections with CF pathogens than classic CF with pancreatic sufficiency.
- Classic CF patients with pancreatic sufficiency had a milder phenotype than those with pancreatic insufficiency.

Critique

- It would be difficult to give the diagnosis of 'CF unlikely' to a parent and almost impossible to reassure them as they will want a yes or no answer to whether their child has a disease. That is, however, an issue for the European diagnostic algorithm rather than this paper.
- This study may help with counselling the CFTR dysfunction group, by providing some guidelines to their potential clinical course which is likely to be milder than classic CF.
- With universal newborn screening in the UK, there is a real issue now when identifying a child with two 'mild' gene mutations but no clinical picture suggestive of CF.

Randomized controlled pilot study – amitryptyline

Riethmüller J, Anthonysamy J, Serra E, Schwab M, Döring G, Gulbins E. Therapeutic efficacy and safety of amitriptyline in patients with cystic fibrosis. *Cell Physiol Biochem* 2009;**24**:65–72

What is already known?

- Ceramide has been show to accumulate in respiratory cells of CF mice in an age-dependent manner, due to an imbalance of acid sphingomyelinase and acid ceramidase.[1]
- Ceramide accumulation results in lung inflammation which is normalized by correction of acid sphingomyelinase.
- The antidepressant amitryptyline blocks acid sphingomyelinase and acid ceramidase. This significantly reduces *Pseudomonas aeruginosa* lung infections in CF mice and prolongs their survival.

Methods

- Randomized double-blinded placebo controlled cross-over study in four adult CF patients received 37.5 mg or placebo twice daily for 14 days.
- Phase IIa cross-over study with three doses (25, 50, 75 mg) or placebo once daily in 19 adults for 28 days (complicated regimen with every patient receiving placebo and two of the doses for 28 days each).
- Outcome was difference in FEV_1 at 14 days.

Results

- FEV_1 improved in 3 of 4 patients in pilot study (relative FEV_1 14.7%, p=0.006), and in the 25 mg group in phase II study (relative FEV_1 4%, $p<0.05$); no differences seen in the 50 mg and 75 mg doses.
- Ceramide levels in the respiratory epithelial cells were decreased significantly in the amitryptyline group.
- Well-tolerated although dry mouth and tiredness noted.

Critique

- Obviously very small numbers but this is proof of principle pilot data.
- Unclear why lung function improved in 25 mg group in phase II study but not at higher doses, as would hope for a dose response (may be type II error).
- Concern that amitryptyline may suppress the acute rise in ceramide that is seen with *Pseudomonas aeruginosa* infectons, which presumably is part of the host defence response.

Case series – methylprenisolone for allergic bronchopulmonary aspergillosis

Cohen-Cymberknoh M, Blau H, Shoseyov D, *et al*. Intravenous monthly pulse methylprednisolone treatment for ABPA in patients with cystic fibrosis. *J Cyst Fibros* 2009;**8**:253–7

What is already known?

- Allergic bronchopulmonary aspergillosis (ABPA) requires corticosteroid therapy. This is usually given as oral prednisolone, usually over several months.
- This therapy is often associated with significant systemic side-effects.
- Monthly pulses of high dose intravenous (IV) methylprednisolone have been used in other diseases with fewer side-effects than oral therapy.
- There has been a report of its use in severe ABPA in four children.[2]

Methods

- Series of nine patients with ABPA aged 7–36 (mean 17.1) years given methylprednisolone.
- Monthly pulses of IV methylprednisolone were given using 10–15 mg/kg per day (maximum dose 1 gm) for 3 days per month with oral itraconazole until ABPA had resolved (using clinical and laboratory parameters).
- They were compared to five patients at another centre aged 3–27 (mean 12.7) years who received oral prednisolone, at 0.5–2 mg/kg/day

Table 1
Side-effects

Adverse effects	*IV pulse methylprednisolone*	*Oral prednisone*
Excessive weight gain (>10%)	1/9	3/5
Hypertension	0/9	2/5
Cushingoid facies	0/9	5/5
Hirsutism	0/9	1/5 (severe)
Acne	0/9	2/5
Emotional instability	1/9 (transient)	2/5 (persistent)
Depression	0/9	1/5 (severe)
Hyperglycemia (in non-CFRD)	0/9	0/4

for 2–4 weeks followed by a tapering dose over 4–12 weeks.

Results

- All patients on methylprednisolone had resolution of their ABPA. Improvements in symptoms, lung function, and reduction in serum IgE were seen after the second course of therapy.
- Therapy was discontinued after 6–10 pulses. One person required further pulses after a relapse following six courses.
- Side-effects were minor (flushing, tiredness, fatigue, agitation, somnolence and myalgia) and disappeared shortly after each pulse therapy.
- All patients on oral therapy showed clinical improvement but 4 of 5 patients required renewing or increasing the dose during the tapering phase.
- Significant side-effects were more common in the oral therapy group (Table 1).

Critique

- Obviously not a randomized controlled trial of IV *vs*. oral therapy (use of a placebo would be unethical) but such a trial is unlikely to take place with sufficient numbers recruited.
- Nevertheless methylprednisolone might be a useful therapeutic option and certainly resolves the issue of non-adherence.
- One drawback, of course, is the need for intravenous therapy hence venous access every month, although not an issue for those with an implantable venous access devices.
- Courses over 6–10 months do seem quite a burden for the patients.

Epidemiology – nutrition and lung function after newborn screening

Lai HJ, Shoff SM, Farrell PM; Wisconsin Cystic Fibrosis Neonatal Screening Group. Recovery of birth weight *z* score within 2 years of diagnosis is positively associated with pulmonary status at 6 years of age in children with cystic fibrosis. *Pediatrics* 2009;**1232**:714–22

What is already known?

- Nearly half of newly-diagnosed CF children have height or weight <5th centile.
- Such malnutrition is associated with poorer clinical outcomes.
- Sixty percent of newly-diagnosed CF children with pancreatic insufficiency respond to therapy with catch-up weight gain, so that within two years they achieve the weight *Z* score comparable to their birth weight (classified as responders).[3]
- Forty percent, however, do not (the non-responders).

Methods

- Sixty-three children with CF and pancreatic insufficiency (but not meconium ileus) in the Wisconsin screening project were studied.
- Followed from 2 to 6 years of age and assessed for nutritional (height and BMI) and pulmonary parameters (symptoms, lung function, chest radiographs and microbiology).

Results

- 41/63 (65%) were classified as responders, 22/63 (35%) as non-responders. Similar proportions of these two groups were diagnosed by newborn screening 68% *vs*. 64%.
- Seventy-one percent of responders maintained their weight recovery to 6 years of age (but note 29% did not).
- Only 32% non-responders achieved substantial growth improvement from 2–6 years.

- Responders had: fewer lung symptoms, e.g. 10% *vs*. 41% daytime cough; better lung function, e.g. FEV_1 100% *vs*. 88% predicted; better chest radiograph scores; similar microbiology.
- Multiple regression analysis showed positive association of lung function was maintained when controlled for infection with (*Pseudomonas aeruginosa* and *Staphylococcus aureus*) and chest radiographs.
- Growth patterns from 2–6 years were not associated with pulmonary measures at 6 years.

Critique

- Shows importance of nutrition and catch-up growth in the 2 years after diagnosis.
- However, this study does not prove that a non-response to early nutrition causes subsequent poor lung function. Like most epidemiological studies, it simply highlights an association, and perhaps poor early growth is an early indicator of worse CF lung disease.

Epidemiology – early lung disease after newborn screening

Sly PD, Brennan S, Gangell C, *et al*.; Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med* 2009;**180**: 146–52

What is already known?

- The expectation of improved outcomes relating to pulmonary disease after the introduction of newborn screening has not been realized.
- Lung disease may be present in CF infants within the first few weeks of life.

Methods

- Fifty-seven infants with median age 3.6 months diagnosed by newborn screening since 2005 in Perth and Melbourne – AREST-CF project.
- CT scan (three-slice inspiratory and expiratory protocol) and bronchoalveolar lavage (BAL) under same general anaesthetic.

Results

- Fifty-four percent were male infants, median age at diagnosis was 28 days.
- Eight-four percent had no respiratory symptoms at time of study.
- Twenty-one percent had bacteria identified on BAL but the majority were asymptomatic.
- Inflammation present in BAL fluid – raised neutrophil count, 77% detectable IL-8, 30% detectable free neutrophil elastase activity. Inflammation increased in symptomatic and infected children.
- CT structural lung disease identified – abnormal in 81%.
- Nineteen percent bronchial dilatation, 45% bronchial wall thickening, 67% gas trapping.
- Most children with structural lung disease had no clinically apparent lung disease.
- Multivariate analysis showed free neutrophil elastase activity associated with structural lung disease.

Critique

- Authors point out lack of control data but I do not see this as a major flaw for BAL, although more of an issue for CT scans, especially as some of the reported abnormalities are relatively subtle.
- Definitions of infection and methods of single lobe BAL may underestimate presence of infection.
- Some of the CT changes may be reversible and helpful that the study did not label some of the changes as bronchiectasis.
- Authors argue for new treatment strategies to realize promise of newborn screening which was that early diagnosis would lead to improved disease outcomes – cannot disagree with that especially for respiratory outcomes.
- Shows that aggressive treatment needs to start early and it is not enough to simply ask the carers how the child is when seen in clinic.

Cochrane systematic reviews – new or substantially amended in 2009 (excluding those which concluded there were no eligible trials to assess)

1. Nash EF, Stephenson A, Ratjen F, Tullis E. Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD007168

There was no evidence to recommend the use of either nebulized or oral thiol derivatives in people with cystic fibrosis.

2. Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1): CD003884 (update of 2005 review)

There are no published data to guide the prescription of chronic oxygen supplementation to people with advanced lung disease due to CF. Short-term oxygen therapy during sleep and exercise improves oxygenation but is associated with modest and probably clinically inconsequential hypercapnia. There are improvements in exercise duration, time to fall asleep and regular attendance at school or work.

3. Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD002769 (update of 2007 review)

Non-invasive ventilation may be a useful adjunct to other airway clearance techniques, particularly in people with CF who have difficulty expectorating sputum. Non-invasive ventilation, used in addition to oxygen, may improve gas exchange during sleep to a greater extent than oxygen therapy alone in moderate to severe disease. These benefits of NIV have largely been demonstrated in single treatment sessions with small numbers of participants. The impact of this therapy on pulmonary exacerbations and disease progression remain unclear.

4. Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD001915 (update of 2000 review)

Evidence from these trials is insufficient to establish whether inhaled corticosteroids are beneficial in CF, but withdrawal in those already taking them has been shown to be safe. There is some evidence they may cause harm in terms of growth. It has not been established whether long-term use is beneficial in reducing lung inflammation, which should improve survival, but it is unlikely this will be proven conclusively in a randomized controlled trial.

5. Morrison L, Agnew J. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD006842

There was no clear evidence that oscillation was a more or less effective intervention overall than other forms of physiotherapy.

6. Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD007298

There is no evidence of benefit or harm in the limited number of small-sized published trials. Adherence to relevant CF guidelines on vitamin D should be considered until further evidence is available.

7. Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD002010

Oral and intravenous bisphosphonates increase bone mineral density in people with CF. Severe bone pain and flu-like symptoms may occur with intravenous agents. Additional trials are needed to determine if bone pain is more common or severe (or both) with the more potent zoledronate and if corticosteroids ameliorate or prevent these adverse events. Trials in larger populations are needed to determine effects on fracture rate and survival.

8. Dharmaraj P, Smyth RL. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD001753

There is currently no evidence from randomized studies that influenza vaccine given to people with CF is of benefit to them.

Guidelines and consensus documents

Therapies

1. Flume PA, Robinson KA, O'Sullivan BP, *et al.*; Clinical Practice Guidelines for Pulmonary

Therapies Committee. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care* 2009;**54**:522–37

The Cystic Fibrosis Foundation established a committee to examine the clinical evidence for efficacy and safety of the variety of airway clearance therapies (ACTs) available. A systematic review identified seven unique reviews and 13 additional controlled trials that addressed one or more of the comparisons of interest and were deemed eligible for inclusion.

They determined that, although there is a paucity of controlled trials that assess the long-term effects of ACTs, the evidence quality overall for their use in CF is fair and the benefit is moderate. They recommended airway clearance be performed on a regular basis in all patients. There are no ACTs demonstrated to be superior to others, so the prescription of ACTs should be individualized. Aerobic exercise was recommended as an adjunctive therapy for airway clearance and for its additional benefits to overall health.

2. Heijerman H, Westerman E, Conway S, Touw D; Gerd Döring for the consensus working group. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2009;**8**:295–315

Inhalation of drugs for the treatment of CF-related lung disease has been proven to be highly effective. Consequently, an increasing number of drugs and devices have been developed for CF lung disease or are currently under development. In this European consensus document they reviewed the current status of inhaled medication in CF, including the mechanisms of action of the various drugs, their modes of administration and indications, their effects on lung function, exacerbation rates, survival and quality of life, as well as side-effects. Specifically, they addressed antibiotics, mucolytics/mucous mobilisers, anti-inflammatory drugs, bronchodilators and combinations of solutions. Additionally, they reviewed the current knowledge on devices for inhalation therapy with regard to optimal particle sizes and characteristics of wet nebulizers, dry powder and metered dose inhalers. Finally, they addressed the subject of testing new devices before market introduction.

Newborn screening and diagnostic issues

3. Castellani C, Southern KW, Brownlee K, *et al*. European best practice guidelines for cystic fibrosis neonatal screening. *J Cyst Fibros* 2009;**8**:153–73

There is wide agreement on the benefits of newborn screening (NBS) for CF in terms of lowered disease severity, decreased burden of care and reduced costs. Risks are mainly associated with disclosure of carrier status and diagnostic uncertainty. When starting a NBS programme for CF it is important to take precautions in order to minimize avoidable risks and maximize benefits. In Europe more than 25 screening programmes have been developed, with quite marked variation in protocol design. However, given the wide geographic, ethnic and economic variations, complete harmonization of protocols is not appropriate. Sweat chloride concentration remains the gold standard for discriminating between NBS false and true positives, but age-related changes in sweat chloride should be taken into account. CF phenotypes associated with less severe disease often have intermediate or normal sweat chloride concentrations.

All newborns identified by NBS should be managed according to internationally accepted guidelines. CF centre care and the availability of necessary medication are essential prerequisites before the introduction of NBS programmes. Programmes should include arrangements for counselling and management of infants where the diagnosis is not clear-cut. Clear explanation to families of the process of screening and of implications of normal and abnormal results is critical. Effective communication is especially important when parents are told that their child is affected or is a carrier. When establishing a NBS programme for CF, attention should be given to ensuring timely and appropriate processing of results, to minimize potential stress for families.

4. Mayell SJ, Munck A, Craig JV, *et al*.; European Cystic Fibrosis Society Neonatal Screening Working GroupA European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. *J Cyst Fibros* 2009;**8**:71–8

Current newborn screening protocols result in recognition of infants with an equivocal diagnosis. A survey of European practice suggested

inconsistencies in the evaluation and management of these infants. This consensus process utilized a modified Delphi method which enabled input of CF specialists from a wide geographical area to a rigorous process that has provided a clear pathway to a consensus statement. A core group produced 21 statements, which were modified over a series of three rounds (including a meeting arranged at the European CF Conference). A final document of 19 statements was produced, all of which achieved a satisfactory level of consensus. The statements cover four themes: sweat testing; further assessments and investigations; review arrangements; and database. This consensus document will provide guidance to CF specialists with established screening programmes and those who are in the process of implementing newborn screening in their region.

5. Dequeker E, Stuhrmann M, Morris MA, *et al*. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – updated European recommendations. *Eur J Hum Genet* 2009;**17**:51–65

The increasing number of laboratories offering molecular genetic analysis of the CFTR gene and the growing use of commercial kits strengthen the need for an update of previous best practice guidelines (published in 2000). The importance of organizing regional or national laboratory networks, to provide both primary and comprehensive CFTR mutation screening, is stressed. Current guidelines focus on strategies for dealing with increasingly complex situations of CFTR testing. Diagnostic flow charts now include testing in CFTR-related disorders and in fetal bowel anomalies. Emphasis is also placed on the need to consider ethnic or geographic origins of patients and individuals, on basic principles of risk calculation and on the importance of providing accurate laboratory reports. Finally, classification of CFTR mutations is reviewed, with regard to their relevance to pathogenicity and to genetic counselling.

Reviewed papers

- Bartlett JR, Friedman KJ, Ling SC, *et al*.; Gene Modifier Study Group. Genetic modifiers of liver disease in cystic fibrosis. *JAMA* 2009;**302**:1076–83
- Goubau C, Wilschanski M, Skalická V, *et al*. Phenotypic characterisation of patients with intermediate sweat chloride values: towards validation of the European diagnostic algorithm for cystic fibrosis. *Thorax* 2009;**64**:683–91
- Riethmüller J, Anthonysamy J, Serra E, *et al*. Therapeutic efficacy and safety of amitriptyline in patients with cystic fibrosis. *Cell Physiol Biochem* 2009;**24**:65–72
- Cohen-Cymberknoh M, Blau H, Shoseyov D, *et al*. Intravenous monthly pulse methylprednisolone treatment for ABPA in patients with cystic fibrosis. *J Cyst Fibros* 2009;**8**:253–7
- Lai HJ, Shoff SM, Farrell PM; Wisconsin Cystic Fibrosis Neonatal Screening Group. Recovery of birth weight z score within 2 years of diagnosis is positively associated with pulmonary status at 6 years of age in children with cystic fibrosis. *Pediatrics* 2009;**1232**:714–22
- Sly PD, Brennan S, Gangell C, *et al*.; Australian Respiratory Early Surveillance Team for Cystic Fibrosis (AREST-CF). Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med* 2009;**180**:
  146–52
- Nash EF, Stephenson A, Ratjen F, *et al*. Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD007168
- Elphick HE, Mallory G. Oxygen therapy for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD003884 (update of 2005 review)
- Moran F, Bradley JM, Piper AJ. Non-invasive ventilation for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD002769 (update of 2007 review)
- Balfour-Lynn IM, Welch K. Inhaled corticosteroids for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD001915 (update of 2000 review)
- Morrison L, Agnew J. Oscillating devices for airway clearance in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(1):CD006842
- Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD007298
- Conwell LS, Chang AB. Bisphosphonates for osteoporosis in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD002010
- Dharmaraj P, Smyth RL. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database Syst Rev* 2009;(4):CD001753

- Flume PA, Robinson KA, O'Sullivan BP, *et al*.; Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care* 2009;**54**:522–37
- Heijerman H, Westerman E, Conway S, *et al*.; for the consensus working group. Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2009;**8**:295–315
- Castellani C, Southern KW, Brownlee K, *et al*. European best practice guidelines for cystic fibrosis neonatal screening. *J Cyst Fibros* 2009;**8**:153–73
- Mayell SJ, Munck A, Craig JV, *et al*.; European Cystic Fibrosis Society Neonatal Screening Working Group. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. *J Cyst Fibros* 2009;**8**:71–8
- Dequeker E, Stuhrmann M, Morris MA, *et al*. Best practice guidelines for molecular genetic diagnosis of cystic fibrosis and CFTR-related disorders – updated European recommendations. *Eur J Hum Genet* 2009;**17**:51–65.

References

1 Teichgräber V, Ulrich M, Endlich N, *et al*. Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis. *Nat Med* 2008;**14**:382–91

2 Thomson JM, Wesley A, Byrnes CA, *et al*. Pulse intravenous methylprednisolone for resistant allergic bronchopulmonary aspergillosis in cystic fibrosis. *Pediatr Pulmonol* 2006;**41**:164–70

3 Shoff SM, Ahn HY, Davis L, *et al*. Wisconsin CF Neonatal Screening Group. Temporal associations among energy intake, plasma linoleic acid, and growth improvement in response to treatment initiation after diagnosis of cystic fibrosis. *Pediat* 2006;**117**:391–400