

## Management of Infants with Cystic Fibrosis: A Summary of the Evidence for the Cystic Fibrosis Foundation Working Group on Care of Infants with Cystic Fibrosis

Karen A. Robinson, PhD, Ian J. Saldanha, MBBS, MPH, and Naomi A. McKoy, BS

**Objective** To inform the development of Cystic Fibrosis (CF) Foundation guidelines on the care of infants with CF, we systematically reviewed the evidence for diagnosis and assessment of pancreatic and pulmonary disorders; management of pancreatic and pulmonary function; management of nutrition and nutritional disorders; and prevention and control of infections.

**Study design** In May-June 2008, we searched The Cochrane Library for existing reviews; and MEDLINE, the National Guideline Clearinghouse, the CF Foundation Clinical Practice Guidelines and Consensus Statements, and the UK CF Trust for existing guidelines. MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Excerpta Medica Database (EMBASE) were searched for primary studies in January 2008. Bibliographies of eligible articles were searched and expert input was sought. We selected English-language articles of any study design that provided original data on any of our questions on infants up to 2 years of age.

**Results** We identified 14 relevant guidelines and 3 Cochrane reviews. Fifty-nine articles (55 primary studies) were included. Only four of these were randomized controlled trials. Sample sizes of infants ranged from 2 to 768 study participants; the median sample size was 24. Of our 21 review topics, 5 topics had only one study while for 5 we identified no relevant studies. We identified one or no primary studies for 20 of 32 review questions.

**Conclusions** There is a paucity of evidence on the care of infants diagnosed with CF. For several of the review questions no guidelines or primary studies were identified, but for other questions, studies limited by weak design and small sample sizes were the only studies identified. With increasing numbers of infants with CF being diagnosed by newborn screening there is an opportunity to study the management of infants diagnosed with CF (*J Pediatr* 2009;155:S94-105).

The Centers for Disease Control and Prevention and the Cystic Fibrosis Foundation recommend routine screening for cystic fibrosis (CF) among newborns.<sup>1</sup> Currently, in the United States, 45 states practice universal newborn screening for CF.<sup>2</sup> It is expected that by December 2009, newborn screening for CF will be performed in all states in the United States.<sup>3</sup> As a result of increased screening, there has been an increase in the number of infants diagnosed with CF, many of whom are symptom free. As of 2007, the median predicted survival age for those with CF in the United States was 37.4 years.<sup>4</sup> The promise of newborn screening is that early diagnosis and initiation of specialized care in infants diagnosed with CF will lead to improved outcomes.<sup>5,6</sup> However, the specifics of such care are unclear.

We were commissioned to review scientific evidence to assist the Cystic Fibrosis Foundation Working Group on Care of Infants with Cystic Fibrosis (CF Foundation Working Group) in making recommendations to the CF community on the care of infants with CF. This article summarizes the findings of systematic reviews of evidence for the benefit of diagnostic measures for pancreatic and pulmonary functional status, management of nutrition and nutritional disorders, management of pancreatic enzymes and disorders, management of pulmonary function, and prevention of infections.

AAP	American Academy of Pediatrics	ICS	Inhaled corticosteroids
ACCP	American College of Chest Physicians	iPFT	Infant pulmonary function test
CF	Cystic fibrosis	MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
CINAHL	Cumulative Index to Nursing and Allied Health Literature	NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
CPT	Chest physiotherapy	PI	Pancreatic insufficient
CT	Computed tomography	PS	Pancreatic sufficient
DHA	Docosahexaenoic acid	RSV	Respiratory syncytial virus
ECC	European Consensus Committee		
EMBASE	Excerpta Medica Database		

From the Department of Medicine, Johns Hopkins University, Baltimore, MD

This study was funded by the Cystic Fibrosis Foundation.

Please see the Author Disclosures at the end of this article.

0022-3476/\$ - see front matter. Copyright © 2009 Mosby Inc. All rights reserved. 10.1016/j.jpeds.2009.09.002

**Table I.** Questions related to key topics on the care of infants with CF

Question number	Question searched
1	What is the evidence for benefit of use of objective measures of pancreatic functional status compared with no use of objective measures of pancreatic functional status in the management of infants with CF?
2(a)	What is the evidence for benefit of use of proprietary, nongeneric pancreatic enzyme preparations compared with use of nonproprietary, generic pancreatic enzyme preparations in the management of infants with CF?
2(b)	What is the evidence for benefit of starting immediate pancreatic enzyme replacement therapy compared with symptom-based pancreatic enzyme replacement therapy in the treatment of infants with CF without PS mutations?
3(a)	What is the evidence for benefit of breast milk feeding compared with any formula feeding in the management of infants with CF?
3(b)	What is the evidence for benefit of breast milk feeding compared with combined breast milk and any formula feeding in the management in infants with CF?
3(c)	What is the evidence for benefit of standard formula feeding compared with other formula feeding in the treatment of infants with CF?
3(d)	What is the evidence for benefit of encouraging positive feeding behaviors compared with not encouraging positive feeding behaviors in the management of infants with CF?
4(a)	What is the evidence for benefit of dietary addition of salt compared with no dietary addition of salt in the treatment of infants with CF?
4(b)	What is the evidence for benefit of supplementation with essential fatty acids compared with no supplementation of essential fatty acids in the treatment of infants with CF?
4(c)	What is the evidence for benefit of supplementation with docosahexaenoic acid (DHA) compared with no supplementation with DHA in the treatment of infants with CF?
4(d)	What is the evidence for benefit of dietary supplementation with zinc compared with no dietary supplementation with zinc in the management of infants with CF?
5	What is the evidence for benefit of vitamin supplementation (B, C, A, D, E, and K) compared with no vitamin supplementation in the treatment of infants with CF?
6	What is the evidence for benefit of routine use of infant pulmonary function tests (iPFT) compared with no routine use of iPFT in the treatment of infants with CF?
7	What is the evidence for benefit of routine use of chest radiography compared with no routine use of chest radiography in the treatment of infants with CF?
8	What is the evidence for benefit of routine use of chest CT scanning compared with no routine use of chest CT scanning in the treatment of infants with CF?
9	What is the evidence for benefit of routine use of oximetry compared with no routine use of oximetry in the treatment of infants with CF?
10	What is the evidence for benefit of routine use of oropharyngeal swabs compared with no routine use of oropharyngeal swabs in the treatment of infants with CF?
11(a)	What is the evidence for benefit of routine use of chest physiotherapy compared with no routine use of chest physiotherapy in the treatment of infants with CF?
11(b)	What is the evidence for benefit of use of chest physiotherapy (CPT) with the patient in a flat position compared with use of CPT with the patient in a head-down position in the treatment of infants with CF?
11(c)	What is the evidence for benefit of routine use of albuterol before chest physiotherapy (CPT) compared with no routine use of albuterol before CPT in the treatment of infants with CF?
12	What is the evidence for benefit of use of dornase alfa (Pulmozyme) compared with no use of dornase alfa in the treatment of infants with CF?
13	What is the evidence for benefit of use of hypertonic saline solution compared with no use of hypertonic saline solution in the treatment of infants with CF?
14	What is the evidence for benefit of long-term use of azithromycin compared with no long-term use of azithromycin in the treatment of infants with CF?
15	What is the evidence for benefit of use of inhaled corticosteroids (ICS) compared with no use of ICS in the treatment of infants with CF?
16	What is the evidence for benefit of use of inhaled tobramycin compared with no use of inhaled tobramycin in the management of <i>Pseudomonas aeruginosa</i> -positive infants with CF?
17(a)	What is the evidence for benefit of use of prophylactic antibiotics compared with no use of prophylactic antibiotics in the prevention of <i>Staphylococcus aureus</i> airway colonization in infants with CF?
17(b)	What is the evidence for benefit of treatment of asymptomatic/initial <i>Staphylococcus aureus</i> airway colonization compared with no treatment of asymptomatic/initial <i>Staphylococcus aureus</i> airway colonization in the treatment of infants with CF?
18	What is the evidence for benefit of treatment of asymptomatic methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) airway colonization compared with no treatment of MRSA colonization in the treatment of infants with CF?
19(a)	What is the evidence for benefit of prophylaxis against <i>Pseudomonas aeruginosa</i> airway colonization compared with no prophylaxis against <i>Pseudomonas aeruginosa</i> airway colonization in the treatment of infants with CF?
19(b)	What is the evidence for benefit of treatment of asymptomatic/initial <i>Pseudomonas aeruginosa</i> airway colonization compared with no treatment of asymptomatic/initial <i>Pseudomonas aeruginosa</i> airway colonization in the treatment of infants with CF?
20	What is the evidence for benefit of seeing patients newly diagnosed with CF separately from other patients cared for in CF clinics compared with not seeing patients newly diagnosed with CF separately from other patients cared for in CF clinics until adequate infection control education has been provided?
21	What is the evidence for benefit of use of respiratory syncytial virus (RSV) prophylaxis compared with no use of RSV prophylaxis in the prevention of infections in infants with CF?

## Methods

### Questions and Role of Funding Source

We worked with the CF Foundation Working Group to develop and refine a series of questions related to key topics on the care of infants with CF (Table I). These questions were designed on the basis of a draft care grid prepared and revised

by the CF Foundation Working Group (after presentation at the North American CF Conference in October 2007).

### Data Sources

**Guidelines and Cochrane Reviews.** For each question, we searched for relevant Cochrane reviews and existing guidelines. The Cochrane Library (Issue 2, 2008) was

Relevant guidelines and Cochrane reviews

Topic	Question Number	Number of Guidelines (Reviews)	Guideline Name or Review Author, Year (see footnote for key)	Reference	Consensus (C) or evidence-based (E)	Specific to individuals with CF? (Y/N)	Included infants ( $\leq 2$ years)? (Y/N/NS)	Recommendations	
-Diagnosis and t of pancreatic function Active tests of pancreatic function	Q1	3	CFF, 1997	12	C	Y	Y	All guidelines recommend that malabsorption and pancreatic function be assessed with objective measures, immediately after diagnosis. All 3 recommend the use of the 3-day fecal fat study.	
			CFF& NASPGHAN, 2002	15	C	Y	Y		
			ECC, 2002	16	C	Y	Y		
-Management of pancreatic and disorders T	Q2	3	CFF, 2008	14	E	Y	Y	All guidelines recommend the use of pancreatic enzyme preparations. Dosing: 2000-4000 lipase units per 120 mL formula or breast milk (CFF) and intake below 10,000 IU/kg/day (ECC, 2002)	
			CFF, 1997	12	C	Y	Y		
			ECC, 2002	16	C	Y	Y		
-Management of nutrition nal disorders ing	Q3 (a)	3	UK CF Trust, 2002-N,	20	C	Y	Y	The UK CF Trust recommends breast milk or whey-based formula from birth, as well as regular reviews and compensation for nutritional needs. ECC, 2002 and CFF & NASPGHAN, 2002 recommend breastfeeding if appropriate, from birth.	
			ECC, 2002	16	C	Y	Y		
			CFF & NASPGHAN, 2002	15	C	Y	Y		
	BM vs. (BM + FM)	Q3 (b)	1	ADA, 2004	11	C	N	Y	Complementary foods are recommended for all infants to meet dietary needs and to develop eating skills. They are recommended after 6 months for breastfed infants.
	Standard FM vs. Other	Q3 (c)	1	ECC, 2002	16	C	Y	Y	Any formula containing adequate energy and supplemented with PERT, is sufficient. Those with poor weight gain should receive additional energy supplements and those with extensive gut resection for mechanical ileus or those with milk intolerance should receive extensively hydrolyzed protein.
Feeding Behavior	Q3 (d)	2	ADA, 2004	11	C	N	Y	The ADA guideline states that while the child are both responsible in a healthful relationship, responsive parenting is the main factor. The CFF guideline recommends behavioral and nutritional counseling.	
			CFF, 2008	14	E	Y	Y		

I. Continued

Topic	Question Number	Number of Guidelines (Reviews)	Guideline Name or Review Author, Year (see footnote for key)	Reference	Consensus (C) or evidence-based (E)	Specific to individuals with CF? (Y/N)	Included infants (≤2 years)? (Y/N/NS)	Recommendations
Salt supplementation	Q4 (a)	1	CFF & NASPGHAN, 2002	15	C	Y	Y	A high-sodium diet is recommended for patients with CF when exposed to heat stress. The introduction of complementary sodium chloride solutions available at pharmacies are more accurate than adding salt to water.
	Q4 (b)	0	—	—	—	—	—	—
	Q4 (c)	(1 review)	(McKarney, 2007)	21	—	Y	N	Insufficient evidence to recommend the use of omega-3 fatty acid supplements for patients with CF.
	Q4 (d)	1	CFF & NASPGHAN, 2002	15	C	Y	Y	An empiric course of zinc supplementation for 6 months for patients with failure to thrive, short stature, or vitamin A deficiency.
Vitamin supplementation	Q5	2	UK CF Trust, 2002-N CFF & NASPGHAN, 2002	20 15	C C	Y Y	Y Y	The UK CF Trust guidelines recommend that CF-PI patients receive vitamins A, D, E, and K from diagnosis; monitor annually, if needed. For patients with PS, cholecalciferol levels annually; supplement if low. The CFF and NASPGHAN guidelines recommend that patients with CF be supplemented with fat and water-soluble vitamins at age-appropriate doses starting from diagnosis. Monitor annually, adjust dose if needed.
	Q6-10	3	UK CF Trust, 2001 ECC, 2005 CFF, 1997	18 17 12	C C C	Y Y Y	Y N N	The UK CF Trust guideline recommends routine pulmonary function testing at routine visits and detailed lung function testing at specialized visits. The UK CF Trust and ECC guidelines recommend oximetry at routine visits. The CFF recommends annual radiographic scoring. The CFF recommends chest radiographs every 2-3 years for clinically stable patients and annually for patients with frequent respiratory infections or declining pulmonary function.

I. Continued

Topic	Question Number	Number of Guidelines (Reviews)	Guideline Name or Review Author, Year (see footnote for key)	Reference	Consensus (C) or evidence-based (E)	Specific to individuals with CF? (Y/N)	Included infants ( $\leq 2$ years)? (Y/N/NS)	Recommendations
Management of pulmonary function chest physiotherapy	Q11	2	ACCP, 2006 CFF, 2008	10	E	Y	N	The ACCP guideline specifically recom chest physiotherapy to increase m clearance. while the CFF guideline recomm clearance therapy for all patients v
				7	E	Y	Y	
Pulmozyme	Q12	1, (1 review)	CFF, 2007 (Jones, 2003)	8 22	E —	Y Y	N N	Pulmozyme treatment is associated w pulmonary function improvement.
Hypertonic saline solution	Q13	1	CFF, 2007	8	E	Y	N	Long-term use of inhaled hypertonic saline solution is recommended to improve pulmonary function and re exacerbations in patients with CF 6 years or older.
Use of azithromycin	Q14	1	CFF, 2007	8	E	Y	N	Long-term use of azithromycin is rec to $\uparrow$ lung function and $\downarrow$ exacerb patients with CF 6 years or older v <i>aeruginosa</i> currently in their airwa
Inhaled corticosteroids	Q15	1	CFF, 2007	8	E	Y	N	Inhaled corticosteroids should not be routinely to improve pulmonary fun reduce exacerbations in patients w 6 years or older without asthma or
Inhaled tobramycin	Q16	1	CFF, 2007	8	E	Y	N	Long-term use of inhaled tobramycin strongly recommended to improve pulmonary function and reduce exacerbations in patients with CF 6 years or older with moderate to severe lung and <i>P. aeruginosa</i> in their airways. with asymptomatic CF or those wi disease, long-term use is recomm reduce exacerbations.
Antibiotic prophylaxis (oral antibiotic treatment)	Q17	1, (1 review)	UK CF Trust, 2002-A (Smyth, 2007)	19	C	Y	Y	The UK CF Trust guideline recommend flucloxacillin after diagnosis for all younger than 2 years of age. The S review concluded that there was in evidence to determine harm or bene anti-staphylococcal antibiotic prop
				23	—	Y	N	

I. Continued

Topic	Question Number	Number of Guidelines (Reviews)	Guideline Name or Review Author, Year (see footnote for key)	Reference	Consensus (C) or evidence-based (E)	Specific to individuals with CF? (Y/N)	Included infants (≤2 years)? (Y/N/NS)	Recommendations
ay n (treatment)	Q18	1	UK CF Trust, 2002-A	19	C	Y	Y	Treatment is best achieved by mupirocin nasal irrigation and strict hospital isolation policies and note sensitivities. If MRSA causes symptoms, nebulized vancomycin (with salbutamol) or Chloramphenicol may be used for exacerbations but not for long-term
nal airway colonization -Prevention/control of	Q19	0	—	—	—	—	—	—
of patients	Q20	1	CFF, 2003	13	C	Y	N	Alert other diagnostic areas and minimize the patient's time in common waiting areas
prophylaxis	Q21	1	AAP, 2003	9	E	Y	Y	Palivizumab is recommended over RSV-IVIG for children younger than 2 years with chronic lung disease. Patients with CF may be at increased risk for RSV infection, but there are no data on the effectiveness of palivizumab in patients with CF.

American Academy of Pediatrics, 2003; ACCP, 2006, American College of Chest Physicians; ADA, 2004, American Dietetic Association; CFF, 1997, CFF Clinical Practice Guidelines of 1997; CFF, 2003, CFF Clinical Practice Guidelines of 2003; CFF Guidelines Committee Guidelines of 2007; CFF, 2008-G CFF, Subcommittee on Growth and Nutrition Guidelines of 2008; CFF, 2008-P, CFF Pulmonary Guidelines Committee Guidelines of 2008; CFF & NASPGHAN, CFF and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Joint Guidelines of 2002; ECC, 2005, European Consensus Committee on Standards of Care for CF Patients Guidelines of 2005; ECC, 2002, European Consensus Committee on Nutrition, 2002; UK CF Trust, 2002-N, UK CF Trust Nutrition Working Group of 2002; UK CF Trust, 2002-A, UK CF Trust Antibiotic Group of 2002; UK CF Trust, 2002-N, UK CF Trust Nutrition Working Group of 2002.

searched for relevant Cochrane systematic reviews. We also sought existing guidelines about infants with CF or, where appropriate, infants without CF or older people with CF. We searched MEDLINE (accessed via PubMed), the National Guideline Clearinghouse, the CF Foundation Clinical Practice Guidelines and Consensus Statements, and the UK CF Trust website in May through June 2008.

**Studies.** Questions addressing management of pulmonary function were included in prior systematic reviews completed for CF Foundation evidence-based guidelines.<sup>7,8</sup> We therefore did not complete additional electronic searches for these questions. For these questions, studies were identified from the prior reviews and from hand searching.

For all other questions, we searched for studies from December 2007 through January 2008 in MEDLINE (accessed via PubMed), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Excerpta Medica Database (EMBASE). We included controlled vocabulary terms and text words for each question, combined with terms for “infants” and “cystic fibrosis.” We scanned reference lists of eligible articles and also sought input from the CF Foundation Working Group.

### Study Selection

Citations were independently screened by 2 reviewers to determine eligibility, first with title and abstract, and subsequently with full-text articles. Disagreements concerning eligibility were resolved by consensus or by a third reviewer. During title and abstract screening, we excluded citations from further consideration if they (1) were not published in English; (2) did not describe a study in human beings; (3) did not include or address CF; (4) provided no original data (ie, review, commentary, etc.); (5) did not include children younger than 6 years of age; (6) addressed benefits/consequences of newborn screening only; and (7) did not address any review questions. At the full-text level, we used the same criteria except that we excluded studies that did not include infants up to 2 years of age. We did not exclude studies on the basis of study design, sample size, study location, or outcomes addressed.

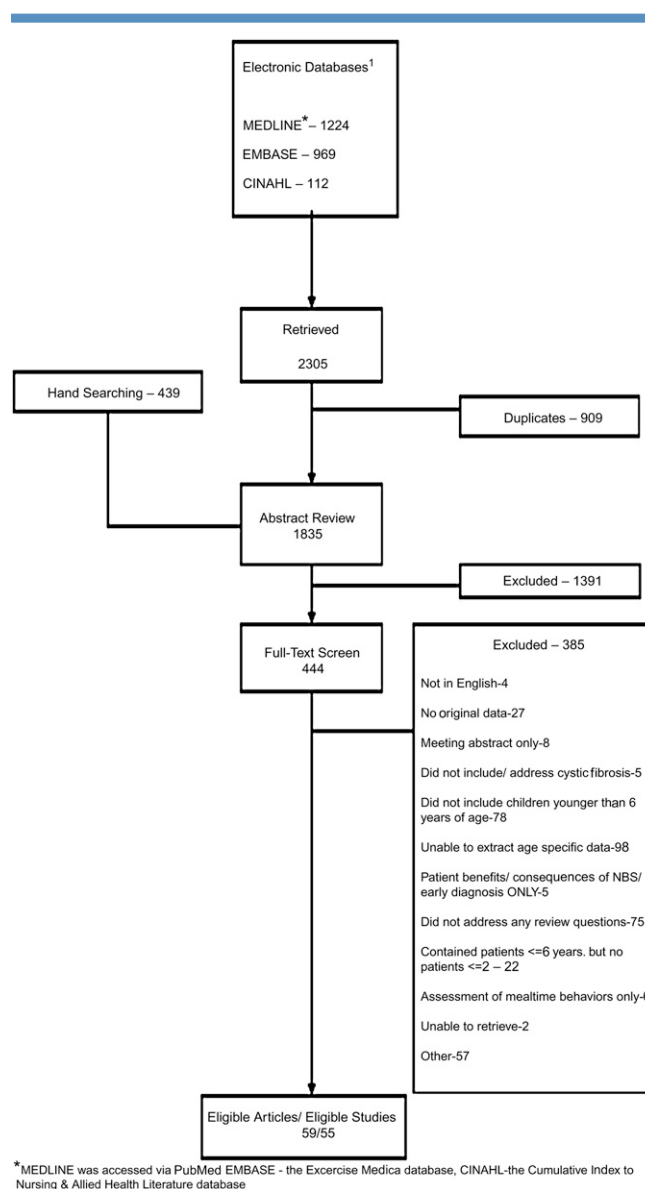
### Data Extraction and Synthesis

Reviewers serially abstracted information about study and participant characteristics, treatment/technique/intervention, outcomes, and conclusions of the study authors. A draft evidence report was provided to the committee 6 weeks before the guidelines meeting that included a summary of any existing guidelines or Cochrane reviews, and a qualitative synthesis (with evidence tables) of the studies we identified. The evidence review was revised on the basis of feedback from the CF Foundation Working Group, and a final review was submitted to the CF Foundation.

## Results

### Guidelines and Cochrane Reviews

We identified 14 relevant guidelines, of which 13 were directed specifically toward individuals with CF.<sup>7-20</sup> These



**Figure.** Summary of Search and Review Process.

guidelines addressed 18 of our 21 review topics. We also identified 3 Cochrane systematic reviews covering 3 topics.<sup>21-23</sup> A summary of relevant guidelines and Cochrane reviews is presented in **Table II**.

### Primary Studies

Our search for primary studies identified 1835 citations, and we excluded 1391 of these at the abstract level. The primary reason for exclusion was that the article did not address any review question (n = 946). At the full-text level 444 articles were screened. The main reasons for exclusions were unable to extract age-specific data (n = 98), did not include children younger than 6 years of age (n = 76), and did not address any review questions (n = 75). The **Figure** provides a summary of our searching and screening process. A list of articles excluded at the full-text level, along with reasons for exclusion, is available on request.

## I. Summary of findings

Topic	Question Number	Number of Studies	Type(s) of Studies (see below for abbreviations)	Number of Participants	Conclusions	
-Diagnosis and t of pancreatic						
ective tests of function	Q1	9	L (Pro) = 2, XS = 6, XS and L (Pro) = 1	179	Fecal fat estimation and fecal chymotrypsin are useful in detecting pancreatic insufficiency. The bentiromide test, steatocrit, and C-13 fat breath test are useful in detecting fat malabsorption.	
-Management of enzymes and						
T -Management of	Q2	2	BA = 2	15	PERT is associated with a decrease in fat malabsorption.	
onal disorders ing	BM vs. FM	Q3 (a)	5	L (Pro) = 2, L (Retro) = 3	1058	Breastfed infants are more likely to have protein malabsorption, hypoalbuminemia, and vitamins D and E deficiencies. But infants breastfed for longer tend to have fewer infections and symptoms, and higher weight-for-age and height-for-age. Gastric emptying time is significantly higher among breastfed infants.
	BM vs. (BM + FM)	Q3 (b)	1	non-RCT = 1	4	
	Standard FM vs. Other	Q3 (c)	5	RCT = 1, non-RCT = 2, non-RXO = 1, L (Retro) = 1	178	Pregestimil, a predigested formula, is associated with significantly higher growth. Linoleic acid is beneficial to infant nutrition and growth. Semielemental formulas are effective for short-term treatment in infants thriving inadequately. Alimentum, a hydrolyzed protein formula, and CF-milk showed no significant improvement in growth. Behavioral interventions and parental counseling are effective in significantly improving the caloric intake of children with growth and feeding problems.
plementation	Feeding Behaviors	Q3 (d)	1	BA = 1	4	
	Salt	Q4 (a)	0	—	—	
	EFA	Q4 (b)	1	non-RCT = 1	76	Formulas rich in linoleic acid showed significant improvements in height-for-age Z scores.
	DHA	Q4 (c)	0	—	—	
plementation	Zinc	Q4 (d)	0	—	—	
		Q5	1	L (Pro) = 1	127	Fat-soluble vitamin deficiency may continue despite vitamin supplementation. Hypoalbuminemia is a risk factor for this deficiency.
-Diagnosis and t of pulmonary						
e of infant PFTs, rays, chest CT scans , oropharyngeal swabs	Q6-10	19	L (Pro) = 9, L (Retro) = 1, XS = 9	761	RVRTC and WBP are useful in detecting early airway abnormalities. PFTs are useful in differentiating between infants with symptomatic CF and control subjects. PFTs can also be effectively used to measure oxygen desaturation during sleep. CXR and X-ray scores are best for assessing bronchopulmonary disease. HRCT scores are useful in detecting airway structural disease in patients with asymptomatic CF. Oropharyngeal cultures do not reliably predict the presence of pathogens in the airways.	
-Management of function st physiotherapy	Q11		RCT = 1, RXO = 2, L (Pro) = 1, BA = 1	85	When comparing use versus no use, chest physiotherapy is associated with a decrease in total resistive work of breathing. When comparing flat versus head-down position, there is conflicting evidence on whether the head-down position contributes to gastroesophageal reflux. When comparing use of albuterol versus combination therapy results in significantly more improvement in pulmonary function than chest physiotherapy alone.	

## II. Continued

Topic	Question Number	Number of Studies	Type(s) of Studies (see below for abbreviations)	Number of Participants	Conclusions
Pulmozyme	Q12	1	RXO = 1	9	Increased airway patency and improved overnight desaturation index occurred after treatment with Pulmozyme.
Hypertonic saline solution	Q13	1	BA = 1	11	Inhalation of a single dose of hypertonic saline solution is safe in infants with CF who are free of a respiratory exacerbation and have had preadministration of a short-acting bronchodilator before saline solution inhalation.
Use of azithromycin	Q14	0	—	—	—
Inhaled corticosteroids	Q15	0	—	—	—
Inhaled tobramycin	Q16	0	—	—	—
Oral airway colonization (prevention/treatment)	Q17	5	RCT = 3, L (Pro) = 2	218	The RCTs reported significantly lower <i>S. aureus</i> cultures in the prophylactic group. In a longitudinal study, fusidic acid and rifampin were successful in treating initial airway colonization in patients with CF.
Oral airway colonization (treatment)	Q18	0	—	—	—
Inhalation airway colonization (prevention/treatment)	Q19	1	L (Retro) = 1	28	Twice-daily inhaled gentamicin can reduce the acquisition of PA.
Prevention/control of airway colonization	Q20	0	—	—	—
Prevention/control of RSV in patients with CF	Q21	2	Retro chart review = 1, Registry data set = 1	166	Fewer hospitalizations occurred among patients who had received RSV prophylaxis.

Pro, prospective; Retro, retrospective; L, Longitudinal study; RSV, respiratory syncytial virus; MRSA, methicillin-resistant *S. aureus*; RVRTC, raised volume rapid thoracic compressions; PFT, pulmonary function test; RXO, randomized cross-over study; WBP, whole body plethysmography; RCT, randomized clinical trial; XS, cross-sectional study.

Fifty-nine articles, reporting on 55 studies, met our criteria.<sup>24-82</sup> Of 21 topics, we identified only 1 study or no studies for 10 topics. For 20 of 32 review questions we identified 1 or no studies.

The studies included 4 randomized controlled trials, 2 randomized crossover studies, 4 nonrandomized controlled trials, 1 nonrandomized crossover study, 16 prospective longitudinal studies, 6 retrospective longitudinal studies, 5 before-after studies, 16 cross-sectional studies, 1 chart review, and 1 registry data set. One study included an initial cross-sectional and subsequent prospective longitudinal design.

Sample sizes ranged from 4 to 768 participants. The median sample size was 38. However, this was for the full studies. In some cases, infants represented a small portion of the sample. Considering only the infants as the sample size, the median sample size of infants with CF was 24 (mean 50, range 2 to 768). The study with the largest sample size was a survey.<sup>30</sup> Excluding this study, there was evidence from 1971 infants and a mean sample size of 37.

### Identification of Evidence Gaps

There were several of the 21 topics (with 32 review questions) for which we identified no or very limited evidence. We found neither existing guidelines nor primary studies for 2 topics: (1) immediate versus symptom-based initiation of pancreatic enzyme replacement therapy and (2) treatment of asymptomatic/initial *Pseudomonas aeruginosa* airway colonization.

For some of our topics, guidelines exist, but we did not find any primary studies. These are

- Dietary supplementation with salt
- Dietary supplementation with DHA
- Dietary supplementation with zinc
- Chronic use of azithromycin
- Use of inhaled corticosteroids
- Use of inhaled tobramycin
- Treatment of asymptomatic/initial *Staphylococcus aureus* airway colonization
- Treatment of initial methicillin-resistant *Staphylococcus aureus* (MRSA) airway colonization
- Separation of newly diagnosed patients

In other cases, we identified primary studies addressing the topics, but no guidelines:

- Dietary supplementation with essential fatty acids
- Routine use of computed tomography (CT scans)
- Routine use of oropharyngeal swabs
- Use of chest physiotherapy in flat versus head-down position
- Routine use of albuterol before chest physiotherapy.

There were some topics for which existing guidelines are not specifically directed toward the CF population. Topics include (1) breast milk–feeding versus combined breast milk–feeding and formula feeding, and (2) encouragement of positive feeding behaviors.

Finally, for the following topics, we identified guidelines for people with CF aged 5 years or older, but not for infants:

- Dietary supplementation with DHA
- Use of chest radiography
- Use of oximetry
- Use of dornase alfa (Pulmozyme)
- Use of hypertonic saline solution
- Long-term use of azithromycin
- Use of inhaled corticosteroids
- Use of inhaled tobramycin
- Separation of newly diagnosed patients

**Table III** provides a summary of findings of all studies identified, by question addressed.

### Discussion

This review highlights gaps in the existing evidence on the care of infants with cystic fibrosis. These gaps meant that the CF Foundation Working Group chose to make consensus rather than evidence-based statements for some topics. The evidence gaps pose significant challenges for the CF community, especially in light of increasing numbers of infants with CF diagnosed by newborn screening. Future research is needed to ensure that management is effective, leading to an early impact on outcomes and further increases in life expectancy in this population. ■

### Author Disclosures

The following authors declare no financial arrangement or affiliation with a corporate organization or a manufacturer of a product discussed in this supplement: Karen A. Robinson, PhD, Ian J. Saldanha, MBBS, MPH, and Naomi A. McKoy, BS

*The authors thank Olaide Adebomi Odelola, MBBS, MPH and Shaon Sengupta, MBBS, MPH, for assistance in reviewing the studies cited in this paper. The authors also acknowledge the guidance of members of the Cystic Fibrosis Foundation Working Group on Care of Infants with Cystic Fibrosis.*

---

Corresponding author: Karen A. Robinson, PhD, Departments of Medicine and Health Sciences Informatics, School of Medicine, Johns Hopkins University, 1830 E Monument Street, Room 8069, Baltimore, MD 21205. E-mail: [krebin@jhmi.edu](mailto:krebin@jhmi.edu).

### References

1. Comeau AM, Accurso FJ, White TB, Campbell PW 3rd, Hoffman G, Parad RB, et al. Guidelines for implementation of cystic fibrosis newborn screening programs: Cystic Fibrosis Foundation workshop report. *Pediatrics* 2007;119:e495-518.
2. Cystic Fibrosis Foundation [homepage on the Internet]. Newborn Screening for Cystic Fibrosis. Available from: [http://www.cff.org/GetInvolved/Advocate/WhyAdvocate/NewbornScreening/#What\\_states\\_do\\_newborn\\_screening\\_for\\_CF?](http://www.cff.org/GetInvolved/Advocate/WhyAdvocate/NewbornScreening/#What_states_do_newborn_screening_for_CF?) Accessed June 1, 2008.
3. Farrell PM. Taking the CF battle to the extremes: healthy starts with newborn screening; North American Cystic Fibrosis Conference; October 25, 2008; Orlando, FL.

4. The Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry, 2006 Annual Data Report. Bethesda: The Cystic Fibrosis Foundation; 2006.
5. Farrell PM, Lai HJ, Li Z, Kosorok MR, Laxova A, Green CG, et al. Evidence on improved outcomes with early diagnosis of cystic fibrosis through neonatal screening: enough is enough!. *J Pediatr* 2005;147:S30-6.
6. Rosenfeld M. Overview of published evidence on outcomes with early diagnosis from large US observational studies. *J Pediatr* 2005;147:S11-4.
7. Flume P, Robinson K, O'Sullivan B, Finder JVR, Willey-Courand D, White TMB, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care* 2009;54:522-37.
8. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr., Willey-Courand DB, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2007;176:957-69.
9. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics* 2003;112:1442-6.
10. McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. *Chest* 2006;129:250S-9S.
11. Butte N, Cobb K, Dwyer J, Graney L, Heird W, Rickard K. The start healthy feeding guidelines for infants and toddlers. *J Am Diet Assoc* 2004;104:442-54.
12. The Cystic Fibrosis Foundation. Clinical practice guidelines for cystic fibrosis. Bethesda: The Cystic Fibrosis Foundation; 1997.
13. Saiman L, Siegel J. Infection control recommendations for patients with cystic fibrosis: microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. *Infect Control Hosp Epidemiol* 2003;24:S6-52.
14. Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *J Am Diet Assoc* 2008;108:832-9.
15. Borowitz D, Baker RD, Stallings V. Consensus report on nutrition for pediatric patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 2002;35:246-59.
16. Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HG, et al. Nutrition in patients with cystic fibrosis: a European Consensus. *J Cyst Fibros* 2002;1:51-75.
17. Kerem E, Conway S, Elborn S, Heijerman H. Standards of care for patients with cystic fibrosis: a European consensus. *J Cyst Fibros* 2005;4:7-26.
18. The CF Trust's Clinical Standards and Accreditation Group. (May 2001). Standards of care. [http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C\\_3000Standards\\_of\\_Care.pdf](http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C_3000Standards_of_Care.pdf). (Accessed June 1, 2008).
19. UK Cystic Fibrosis Trust [homepage on the Internet]. [September 2002]. UK Cystic Fibrosis Trust Antibiotic Group. Antibiotic treatment for cystic fibrosis. Available from: [http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C\\_3200Antibiotic\\_Treatment.pdf](http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C_3200Antibiotic_Treatment.pdf). Accessed June 1, 2008.
20. UK Cystic Fibrosis Trust [homepage on the Internet]. [April 2002]. UK Cystic Fibrosis Trust Nutrition Working Group. Nutritional management in cystic fibrosis. A consensus report. Available from: [http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C\\_3500Nutritional\\_Management.pdf](http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/C_3500Nutritional_Management.pdf). Accessed June 1, 2008.
21. McKarney C, Everard M, N'Diaye T. Omega-3 fatty acids (from fish oils) for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD002201. DOI: 10.1002/14651858.CD002201.pub2. 2007;CD002201.
22. Jones AP, Wallis CE, Kearney CE. Dornase alpha for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001127. DOI: 10.1002/14651858.CD001127.
23. Smyth A, Walters S. Prophylactic antibiotics for cystic fibrosis. *Cochrane Database of Systematic Reviews*: Reviews 2003, Issue 3. Art. No.: CD001912. DOI: 10.1002/14651858.CD001912.
24. Giebels K, Marcotte JE, Podoba J, Rousseau C, Denis MH, Fauvel V, et al. Prophylaxis against respiratory syncytial virus in young children with cystic fibrosis. *Pediatr Pulmonol* 2007;43:169-74.
25. Colombo C, Costantini D, Zazzeron L, Faelli N, Russo MC, Ghisleni D, et al. Benefits of breastfeeding in cystic fibrosis: a single-centre follow-up survey. *Acta Paediatrica* 2007;96:1228-32.
26. Subbarao P, Balkovec S, Solomon M, Ratjen F. Pilot study of safety and tolerability of inhaled hypertonic saline in infants with cystic fibrosis. *Pediatr Pulmonol* 2007;42:471-6.
27. Lum S, Gustafsson P, Ljungberg H, Hulskamp G, Bush A, Carr SB, et al. Early detection of cystic fibrosis lung disease: multiple-breath washout versus raised volume tests. *Thorax* 2007;62:341-7.
28. Martinez TM, Llapur CJ, Williams TH, Coates C, Gunderman R, Cohen MD, et al. High-resolution computed tomography imaging of airway disease in infants with cystic fibrosis. *Am J Respir Crit Care Med* 2005;172:1133-8.
29. Berge MT, Wiel E, Tiddens HA, Merkus PJ, Hop WC, de Jongste JC. DNase in stable cystic fibrosis infants: a pilot study. *J Cyst Fibros* 2003;2:183-8.
30. Parker EM, O'Sullivan BP, Shea JC, Regan MM, Freedman SD. Survey of breast-feeding practices and outcomes in the cystic fibrosis population. *Pediatr Pulmonol* 2004;37:362-7.
31. Farrell PM, Li Z, Kosorok MR, Laxova A, Green CG, Collins J, et al. Longitudinal evaluation of bronchopulmonary disease in children with cystic fibrosis. *Pediatr Pulmonol* 2003;36:230-40.
32. Button BM, Heine RG, Catto-Smith AG, Olinsky A, Phelan PD, Ditchfield MR, et al. Chest physiotherapy in infants with cystic fibrosis: to tip or not? A five-year study. *Pediatr Pulmonol* 2003;35:208-13.
33. 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.
34. Heinzl 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;33:32-7.
35. Feranchak AP, Sontag MK, Wagener JS, Hammond KB, Accurso FJ, Sokol RJ. Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen. *J Pediatr* 1999;135:601-10.
36. Ellis L, Kalnins D, Corey M, Brennan J, Pencharz P, Durie P. Do infants with cystic fibrosis need a protein hydrolysate formula? A prospective, randomized, comparative study. *J Pediatr* 1998;132:270-6.
37. van Egmond AW, Kosorok MR, Kosciak R, Laxova A, Farrell PM. Effect of linoleic acid intake on growth of infants with cystic fibrosis. *Am J Clin Nutr* 1996;63:746-52.
38. Beardsmore CS. Lung function from infancy to school age in cystic fibrosis. *Arch Dis Child* 1995;73:519-23.
39. Turner DJ, Lanteri CJ, LeSouef PN, Sly PD. Improved detection of abnormal respiratory function using forced expiration from raised lung volume in infants with cystic fibrosis. *Eur Respir J* 1994;7:1995-9.
40. Beardsmore CS, Thompson JR, Williams A, McArdle EK, Gregory GA, Weaver LT, et al. Pulmonary function in infants with cystic fibrosis: the effect of antibiotic treatment. *Arch Dis Child* 1994;71:133-7.
41. Weaver LT, Green MR, 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;70:84-9.
42. McClean P, Harding M, Coward WA, Green MR, Weaver LT. Measurement of fat digestion in early life using a stable isotope breath test. *Arch Dis Child* 1993;69:366-70.
43. Tepper RS, Montgomery GL, Ackerman V, Eigen H. Longitudinal evaluation of pulmonary function in infants and very young children with cystic fibrosis. *Pediatr Pulmonol* 1993;16:96-100.
44. Bronstein MN, Sokol RJ, Abman SH, Chatfield BA, Hammond KB, Hambidge KM, et al. Pancreatic insufficiency, growth, and nutrition in infants identified by newborn screening as having cystic fibrosis. *J Pediatr* 1992;120:533-40.
45. Greer R, Shepherd R, Cleghorn G, Bowling FG, Holt T. Evaluation of growth and changes in body composition following neonatal

- diagnosis of cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1991;13:52-8.
46. Singer LT, Nofer JA, Benson-Szekely LJ, Brooks LJ. Behavioral assessment and management of food refusal in children with cystic fibrosis. *J Dev Behav Pediatr* 1991;12:115-20.
  47. Holliday KE, Allen JR, Waters DL, Gruca MA, Thompson SM, Gaskin KJ. Growth of human milk-fed and formula-fed infants with cystic fibrosis. *J Pediatr* 1991;118:77-9.
  48. Lynch DA, Brasch RC, Hardy KA, Webb WR. Pediatric pulmonary disease: assessment with high-resolution ultrafast CT. *Radiology* 1990;176:243-8.
  49. Sokol RJ, Reardon MC, Accurso FJ, Stall C, Narkewicz M, Abman SH, et al. Fat-soluble-vitamin status during the first year of life in infants with cystic fibrosis identified by screening of newborns. *Am J Clin Nutr* 1989;50:1064-71.
  50. Hardy KA, Wolfson MR, Schidlow DV, Shaffer TH. Mechanics and energetics of breathing in newly diagnosed infants with cystic fibrosis: effect of combined bronchodilator and chest physical therapy. *Pediatr Pulmonol* 1989;6:103-8.
  51. Kraemer R. Early detection of lung function abnormalities in infants with cystic fibrosis. *J R Soc Med* 1989;82(Suppl 16):21-5.
  52. Maayan C, Bar-Yishay E, Yaacobi T, Marcus Y, Katznelson D, Yahav Y, et al. Immediate effect of various treatments on lung function in infants with cystic fibrosis. *Respiration* 1989;55:144-51.
  53. Beardsmore CS, Bar-Yishay E, Maayan C, Yahav Y, Katznelson D, Godfrey S. Lung function in infants with cystic fibrosis. *Thorax* 1988;43:545-51.
  54. Tepper RS, Hiatt P, Eigen H, Scott P, Grosfeld J, Cohen M. Infants with cystic fibrosis: pulmonary function at diagnosis. *Pediatr Pulmonol* 1988;5:15-8.
  55. Farrell PM, Mischler EH, Sondel SA, Palta M. Predigested formula for infants with cystic fibrosis. *J Am Diet Assoc* 1987;87:1353-6.
  56. Tepper RS, Hiatt PW, Eigen H, Smith J. Total respiratory system compliance in asymptomatic infants with cystic fibrosis. *Am Rev Resp Dis* 1987;135:1075-9.
  57. Canciani M, Mastella G. Absorption of a new semielemental diet in infants with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1985;4:735-40.
  58. Harrison CJ, Marks MI, Welch DF, Sharma BB, Baker D, Dice J. A multicenter comparison of related pharmacologic features of cephalixin and dicloxacillin given for two months to young children with cystic fibrosis. *Pediatr Pharmacol* 1985;5:7-16.
  59. Bellentani S, Grisendi A, Rinaldi M, Bertolani P, Costa G, Agostini M, et al. BT-Paba test in the diagnosis of pancreatic exocrine insufficiency in cystic fibrosis: urinary and serum determinations compared. *Eur J Pediatr* 1984;143:145-8.
  60. Gillard BK, Cox KL, Pollack PA, Geffner ME. Cystic fibrosis serum pancreatic amylase. Useful discriminator of exocrine function. *Am J Dis Child* 1984;138:577-80.
  61. Durie PR, Largman C, Brodrick JW, Johnson JH, Gaskin KJ, Forstner GG, et al. Plasma immunoreactive pancreatic cationic trypsinogen in cystic fibrosis: a sensitive indicator of exocrine pancreatic dysfunction. *Pediatr Res* 1981;15:1351-5.
  62. Cavell B. Gastric emptying in infants with cystic fibrosis. *Acta Paediatr Scand* 1981;70:635-8.
  63. Durie PR, Newth CJ, Forstner GG, Gall DG. Malabsorption of medium-chain triglycerides in infants with cystic fibrosis: correction with pancreatic enzyme supplement. *J Pediatr* 1980;96:862-4.
  64. Godfrey S, Mearns M, Howlett G. Serial lung function studies in cystic fibrosis in the first 5 years of life. *Arch Dis Child* 1978;53:83-5.
  65. Simmonds EJ, Wall CR, Wolfe SP, Littlewood JM. A review of infant feeding practices at a regional cystic fibrosis unit. *J Hum Nutr Diet* 1994;7:31-8.
  66. Armstrong DS, Grimwood K, Carlin JB, Carzino R, Olinsky A, Phelan PD. Bronchoalveolar lavage or oropharyngeal cultures to identify lower respiratory pathogens in infants with cystic fibrosis. *Pediatr Pulmonol* 1996;21:267-75.
  67. 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.
  68. Ranganathan SC, Bush A, Dezateux C, Carr SB, Hoo AF, Lum S, et al. Relative ability of full and partial forced expiratory maneuvers to identify diminished airway function in infants with cystic fibrosis. *Am J Resp Crit Care Med* 2002;166:1350-7.
  69. Hendeles L, Dorf A, Stecenko A, Weinberger M. Treatment failure after substitution of generic pancrelipase capsules. Correlation with in vitro lipase activity. *JAMA* 1990;263:2459-61.
  70. Gaskin K, Waters D, Dorney S, Gruca M, O'Halloran M, Wilcken B. Assessment of pancreatic function in screened infants with cystic fibrosis. *Pediatr Pulmonol Suppl* 1991;7:69-71.
  71. Wright GL, Harper J. Fusidic acid and lincomycin therapy in staphylococcal infections in cystic fibrosis. *Lancet* 1970;1:9-14.
  72. Villa MP, Pagani J, Lucidi V, Palamides S, Ronchetti R. Nocturnal oximetry in infants with cystic fibrosis. *Arch Dis Child* 2001;84:50-4.
  73. Phillips GE, Pike SE, Rosenthal M, Bush A. Holding the baby: head downwards positioning for physiotherapy does not cause gastro-oesophageal reflux. *Eur Resp J* 1998;12:954-7.
  74. Colombo C, Maiavacca R, Ronchi M, Consalvo E, Amoretti M, Giunta A. The steatocrit: a simple method for monitoring fat malabsorption in patients with cystic fibrosis. *J Pediatr Gastroenterol Nutr* 1987;6:926-30.
  75. Remtulla MA, Durie PR, Goldberg DM. Stool chymotrypsin activity measured by a spectrophotometric procedure to identify pancreatic disease in infants. *Clin Biochem* 1986;19:341-7.
  76. Abman SH, Ogle JW, Harbeck RJ, Butler-Simon N, Hammond KB, Accurso FJ. Early bacteriologic, immunologic, and clinical courses of young infants with cystic fibrosis identified by neonatal screening. *J Pediatr* 1991;119:211-7.
  77. Hudson VL, Wielinski CL, Regelman WE. Prognostic implications of initial oropharyngeal bacterial flora in patients with cystic fibrosis diagnosed before the age of two years. *J Pediatr* 1993;122:854-60.
  78. Ranganathan SC, Stocks J, Dezateux C, Bush A, Wade A, Carr S, et al. The evolution of airway function in early childhood following clinical diagnosis of cystic fibrosis. *Am J Resp Crit Care Med* 2004;169:928-33.
  79. Speer ME, Fernandes CJ, Boron M, Groothuis JR. Use of palivizumab for prevention of hospitalization as a result of respiratory syncytial virus in infants with cystic fibrosis. *Pediatr Infect Dis J* 2008;27:559-61.
  80. Button BM, Heine RG, Catto-Smith AG, Phelan PD, Olinsky A. Postural drainage and gastro-oesophageal reflux in infants with cystic fibrosis. *Arch Dis Child* 1997;76:148-50.
  81. Watkins JB, Schoeller DA, Klein PD, Ott DG, Newcomer AD, Hofmann AF. 13C-trioctanoin: a nonradioactive breath test to detect fat malabsorption. *J Lab Clin Med* 1977;90:422-30.
  82. Button BM, Heine RG, Catto-Smith AG, Phelan PD, Olinsky A. Chest physiotherapy, gastro-oesophageal reflux, and arousal in infants with cystic fibrosis. *Arch Dis Child* 2004;89:435-9.