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.[1] Currently, in the United States, 45 states practice universal newborn screening for CF.[2] It is expected that by December 2009, newborn screening for CF will be performed in all states in the United States.[3] 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.[4] The promise of newborn screening is that early diagnosis and initiation of specialized care in infants diagnosed with CF will lead to improved outcomes.[5,6] 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 *Staphylococcus aureus*
CINAHL	Cumulative Index to Nursing and Allied Health Literature	NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
CPT	Chest physiotherapy		
CT	Computed tomography		
DHA	Docosahexaenoic acid	PI	Pancreatic insufficient
ECC	European Consensus Committee	PS	Pancreatic sufficient
		RSV	Respiratory syncytial virus
EMBASE	Excerpta Medica Database		

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

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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 *Pseudomonas aeruginosa*–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 *Staphylococcus aureus* airway colonization in infants with CF?
17(b)	What is the evidence for benefit of treatment of asymptomatic/initial *Staphylococcus aureus* airway colonization compared with no treatment of asymptomatic/initial *Staphylococcus aureus* airway colonization in the treatment of infants with CF?
18	What is the evidence for benefit of treatment of asymptomatic methicillin-resistant *Staphylococcus aureus* (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 *Pseudomonas aeruginosa* airway colonization compared with no prophylaxis against *Pseudomonas aeruginosa* airway colonization in the treatment of infants with CF?
19(b)	What is the evidence for benefit of treatment of asymptomatic/initial *Pseudomonas aeruginosa* airway colonization compared to no treatment of asymptomatic/initial *Pseudomonas aeruginosa* 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 (≤2 years)? (Y/N/NS)	Recommendations
–Diagnosis and t of pancreatic function									
ctive tests of pancreatic function		Q1	3	CFF, 1997 CFF& NASPGHAN, 2002 ECC, 2002	12 15 16	C C C	Y Y Y	Y Y Y	All guidelines recommend that malabso and pancreatic function be assessed objective measures, immediately after diagnosis. All 3 recommend the use of the 3-day fecal fat study.
–Management of pancreatic nd disorders									
T		Q2	3	CFF, 2008 CFF, 1997 ECC, 2002	14 12 16	E C C	Y Y Y	Y Y Y	All guidelines recommend the use of proprietary pancreatic enzyme preparations. Dosing: 2000-4000 lipa units per 120 mL formula or beast m (CFF) and intake below 10,000 IU/kg/ (ECC, 2002)
–Management of nutrition onal disorders									
ling	BM vs. FM	Q3 (a)	3	UK CF Trust, 2002-N, ECC, 2002 CFF & NASPGHAN, 2002	20 16 15	C C C	Y Y Y	Y Y Y	The UK CF Trust recommends breast m or whey-based formula from birth, as as regular reviews and compensation nutritional needs. ECC, 2002 and CFF NASPGHAN, 2002 recommend breast if appropriate, from birth.
	BM vs. (BM + FM)	Q3 (b)	1	ADA, 2004	11	C	N	Y	Complementary foods are recommende for all infants to meet dietary needs a develop eating skills. They are recom after 6 months for breastfed infants.
	Standard FM vs. Other	Q3 (c)	1	ECC, 2002	16	C	Y	Y	Any formula containing adequate energy supplemented with PERT, is sufficien Those with poor weight gain should r additional energy supplements and th with extensive gut resection for meco ileus or those with milk intolerance s receive extensively hydrolyzed protei
	Feeding Behavior	Q3 (d)	2	ADA, 2004 CFF, 2008	11 14	C E	N Y	Y Y	The ADA guideline states that while the child are both responsible in a health relationship, responsive parenting is t main factor. The CFF guideline recom behavioral and nutritional counseling

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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
plementation	Salt	Q4 (a)	1	CFF & NASPGHAN, 2002	15	C	Y	Y	A high-sodium diet is recommended with CF when exposed to heat stre the introduction of complementary Sodium chloride solutions availabl pharmacies are more accurate tha adding salt to water.
		Q4 (b)	0	—	—	—	—	—	—
		Q4 (c)	(1 review)	(McKarney, 2007)	21	—	Y	N	Insufficient evidence to recommend use of omega-3 fatty acid supplen patients with CF.
		Q4 (d)	1	CFF& NASPGHAN, 2002	15	C	Y	Y	An empiric course of zinc supplemen 6 months for patients with failure short stature, or vitamin A deficien
		Q5	2	UK CF Trust, 2002-N	20	C	Y	Y	The UK CF Trust guidelines recomme
tation				CFF & NASPGHAN, 2002	15	C	Y	Y	CF-PI patients receive vitamins A, from diagnosis; monitor annually, if needed. For patients with PS, ch levels annually; supplement if low and NASPGHAN guidelines recomm patients with CF be supplemented fat and water-soluble vitamins at age-appropriate doses starting fro Monitor annually, adjust dose if ne
-Diagnosis and t of function									
e of infant PFTs, graphy, chest CT metry, aryngeal swabs		Q6-10	3	UK CF Trust, 2001	18	C	Y	Y	The UK CF Trust guideline recommen
				ECC, 2005	17	C	Y	N	pulmonary function testing at routi
				CFF, 1997	12	C	Y	N	visits and detailed lung function tes The UK CF Trust and ECC guidelin recommend oximetry at routine vis annual radiographic scoring. The CF recommends chest radiographs ev years for clinically stable patients or annually for patients with frequ infections or declining pulmonary f

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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
–Management of pulmonary function								
st physiotherapy	Q11	2	ACCP, 2006	10	E	Y	N	The ACCP guideline specifically recor
			CFF, 2008	7	E	Y	Y	chest physiotherapy to increase m clearance. while the CFF guideline recommer clearance therapy for all patients v
mozyme	Q12	1, (1 review)	CFF, 2007	8	E	Y	N	Pulmozyme treatment is associated v
			(Jones, 2003)	22	—	Y	N	pulmonary function improvement.
ertonic 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 ycin	Q14	1	CFF, 2007	8	E	Y	N	Long-term use of azithromycin is rec to ↑ lung function and ↓ exacerba patients with CF 6 years or older v *aeruginosa* currently in their airwa
led corticosteroids	Q15	1	CFF, 2007	8	E	Y	N	Inhaled corticosteroids should not be routinely to improve pulmonary fur reduce exacerbations in patients v 6 years or older without asthma or
led 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 older with moderate to severe lung and *P. aeruginosa* in their airways. with asymptomatic CF or those wi disease, long-term use is recomm reduce exacerbations.
ccal	Q17	1, (1 review)	UK CF Trust, 2002-A	19	C	Y	Y	The UK CF Trust guideline recommend
onization /treatment)			(Smyth, 2007)	23	—	Y	N	flucloxacillin after diagnosis for all younger than 2 years of age. The Sr review concluded that there was in evidence to determine harm or bene anti-staphylococcal antibiotic prop

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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 mupiro hospital isolation policies and note sensitivities. If MRSA causes symp nebulized vancomycin (with salbut 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 mini the patient's time in common wait
prophylaxis	Q21	1	AAP, 2003	9	E	Y	Y	Palivizumab is recommended over RSV-IVIG for children younger years with chronic lung disease. Patients with CF may be at increas for RSV infection, but there are no effectiveness of palivizumab in pa with CF.

erican 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 20
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 Ameri
enterology, 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*
nical Standards and Accreditation Group of 2001; *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.[7,8] 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.[7-20] These guidelines addressed 18 of our 21 review topics. We also identified 3 Cochrane systematic reviews covering 3 topics.[21-23] A summary of relevant guidelines and Cochrane reviews is presented in Table II.

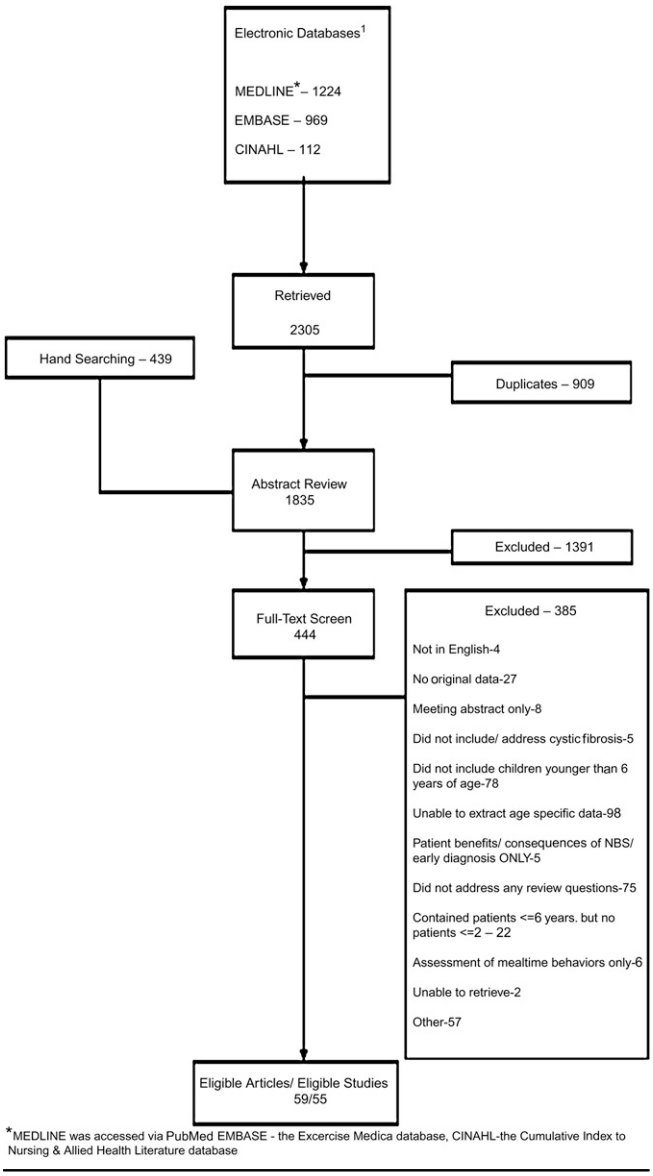

Figure. Summary of Search and Review Process.

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.

II. 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						
ctive 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 pancrea insufficiency. The bentiromide test, steatocrit, and C-13 fat breath test ar detecting fat malabsorption.
–Management of enzymes and						
T		Q2	2	BA = 2	15	PERT is associated with a decrease in fat malabsorption.
–Management of						
nal disorders ing	BM vs. FM	Q3 (a)	5	L (Pro) = 2, L (Retro) = 3	1058	Breastfed infants are more likely to have protein malabsorption, hypoalbum and vitamins D and E deficiencies. But infants breastfed for longer tend t fewer infections and symptoms, and higher weight-for-age and height-fo
	BM vs. (BM + FM)	Q3 (b)	1	non-RCT = 1	4	Gastric emptying time is significantly higher among breastfed infants.
	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 gr Linoleic acid is beneficial to infant nutrition and growth. Semielemental c effective for short-term treatment in infants thriving inadequately. Alimen hydrolyzed protein formula, and CF-milk showed no significant improvem
	Feeding Behaviors	Q3 (d)	1	BA = 1	4	Behavioral interventions and parental counseling are effective in significantl improving the caloric intake of children with growth and feeding problem
plementation	Salt	Q4 (a)	0	—	—	—
	EFA	Q4 (b)	1	non-RCT = 1	76	Formulas rich in linoleic acid showed significant improvements in height-for Z scores.
	DHA	Q4 (c)	0	—	—	—
	Zinc	Q4 (d)	0	—	—	—
plementation		Q5	1	L (Pro) = 1	127	Fat-soluble vitamin deficiency may continue despite vitamin supplementatio 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 an can differentiate between infants with symptomatic CF and control subje can also be effectively used to measure oxygen desaturation during slee X-ray scores are best for assessing bronchopulmonary disease. HRCT sc useful in detecting airway structural disease in patients with asymptomat Oropharyngeal cultures do not reliably predict the presence of pathogens airways.
–Management of function st physiotherapy		Q11		RCT = 1, RX0 = 2, L (Pro) = 1, BA = 1	85	When comparing use versus no use, chest physiotherapy is associated with decrease in total resistive work of breathing. When comparing flat versus position, there is conflicting evidence on whether the head-down position contributes to gastroesophageal reflux. When comparing use of albuterol ve combination therapy results in significantly more improvement in pulmonary than chest physiotherapy alone.

II. Continued

Topic	Question Number	Number of Studies	Type(s) of Studies (see below for abbreviations)	Number of Participants	Conclusions
mozyme	Q12	1	RXO = 1	9	Increased airway patency and improv overnight desaturation index occur after treatment with Pulmozyme.
ertonic saline solution	Q13	1	BA = 1	11	Inhalation of a single dose of hyperto solution is safe in infants with CF free of a respiratory exacerbation have had preadministration of a sh bronchodilator before saline soluti inhalation.
use of azithromycin	Q14	0	—	—	—
led corticosteroids	Q15	0	—	—	—
led tobramycin	Q16	0	—	—	—
ccal airway colonization /treatment)	Q17	5	RCT = 3, L (Pro) = 2	218	The RCTs reported significantly lower *aureus* cultures in the prophylactic longitudinal study, fusidic acid and were successful in treating initial colonization in patients with CF.
ay colonization (treatment)	Q18	0	—	—	—
nal airway colonization /treatment) –Prevention/control of	Q19	1	L (Retro) = 1	28	Twice-daily inhaled gentamicin can c acquisition of PA
of patients	Q20	0	—	—	—
prophylaxis	Q21	2	Retro chart review = 1, Registry data set = 1	166	Fewer hospitalizations occurred amon who had received RSV prophylaxis

r study; *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-o
BP, whole body plethysmography; *RCT,* randomized clinical trial; *XS,* cross-sectional study.

Fifty-nine articles, reporting on 55 studies, met our criteria.[24-82] 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.[30] 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

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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: krobin@jhmi.edu.

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