ELSEVIER

Journal of Cystic Fibrosis 9 (2010) 323 – 329

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Guidelines on the early management of infants diagnosed with cystic fibrosis following newborn screening☆

Isabelle Sermet-Gaudelus [a], Sarah J. Mayell [b], Kevin W. Southern [b,*]

[a] CRCM, Hopital Necker-Enfants Malades, INSERM U 845, Universite Parsi Descartes, 149 Rue de Sevres, Paris 75015, France
[b] Institute of Child Health, University of Liverpool, Alder Hey Children's Hospital, Eaton Road, Liverpool, L12 2AP, United Kingdom

Received 5 November 2009; received in revised form 30 March 2010; accepted 30 April 2010

Abstract

Background: Successful implementation of newborn screening (NBS) for cystic fibrosis (CF) depends on robust protocols, good communication and appropriate management of recognised infants. In response to current varied practice, the ECFS Neonatal Screening Working Group developed a consensus on the early management of these infants using the Delphi methodology.
Methods: Following detailed literature review, statements were generated by a core group of experts and then assessed by a larger group using modified Delphi methodology.
Results: Forty-one statements were written by the core group. Eighty-six CF specialists contributed to the modified Delphi process. During three rounds, extra statements were added and consensus achieved on 44 (one statement did not achieve consensus).
Conclusions: These statements will provide a framework for the management of screened infants in the first year of life. This process highlights the paucity of evidence on which to base management of these infants. To improve this situation, it is important that each infant with CF identified through NBS has opportunity to be included in a randomised controlled trial.

Keywords: Cystic fibrosis; Newborn screening; Delphi methodology; Guidelines; Infants; Management

1. Introduction

The successful expansion of newborn screening for cystic fibrosis (CF) across Europe has highlighted the need for clear guidance on the management of screen-positive infants, based on the best available evidence [1,2]. Current practice has evolved through experiential knowledge and a previous survey suggests wide variability across regions and countries [3]. There is good evidence to support newborn screening as a valid undertaking, particularly with respect to early nutritional benefits [1,4–8] but the validity of screening is undermined if appropriate management is not available [9].

This project was undertaken under the auspices of the European CF Society Neonatal Screening Working Group and involved three stages: a review and grading of available evidence; generation of draft guideline statements by a core group of experts and, finally, review and modification of those statements through a modified Delphi consensus process.

The Delphi methodology allows the development of a consensus on actions when a lack of published evidence is available to guide practice [10]. This methodology has been recognised by numerous healthcare authorities, including the World Health Organisation, as an important and valid technique for establishing consensus. The strengths of the process are inclusivity, relative anonymity (giving exposure to the quiet voice) and economy (can be conducted primarily through email correspondence). The drawbacks are that it is time consuming and generates a large amount of data, which needs careful analysis.

The aim of this project was to produce evidence based guidelines on the management during the first year of life of infants with CF diagnosed through newborn screening.

☆ Data presented at 32nd ECFS meeting, Brest, France: Sermet-Gaudelus I, Mayell SJ, Southern KW. Towards a consensus on the early management of infants identified with cystic fibrosis following newborn screening (NBS) *J Cyst Fibros* 2009;8 suppl 2:S11 (abstract 41).

* Corresponding author. Tel.: +44 151 2933536; fax: +44 151 2525456.
E-mail address: kwsouth@liv.ac.uk (K.W. Southern).

1569-1993/$ - see front matter.
doi:10.1016/j.jcf.2010.04.008

2. Methods

A list of topics was defined by a core group and a comprehensive search undertaken for published and unpublished literature on these topics (IS). After completing this process statements were generated and graded according to the recommendations of the Scottish Intercollegiate Guidelines Network (SIGN) (IS and KWS) [11].

These statements were then further reviewed and modified by a core group of CF experts. Statements were divided into General, Nutritional and Respiratory. Nutritional and Respiratory statements were further divided into three classes of statement; 1) Monitoring, 2) Preventive and 3) Reactive.

All members of the European CF Society (ECFS) were invited to contribute to the modified Delphi methodology. The Delphi process was overseen by a facilitating group (IS, SM and KWS). This group sought further advice from experts on comments that arose during the Delphi process.

Inclusion was restricted to respondents in Europe and Australasia, so as not to replicate work being undertaken for North America (personal communication, P Farrell and D Borowitz). In addition, health professionals from different disciplines (for example, dietetics and physiotherapy) were approached directly to ensure multidisciplinary representation.

Participants were sent the list of statements and asked whether they agreed, disagreed or were unable to comment with each. If they disagreed they were asked to provide a reason and/or an alternative statement. References were also requested, in case trials had been overlooked in the initial search strategy.

We determined that 80% agreement would determine an adequate consensus on a statement [12]. However, even if consensus was achieved, comments were still considered and incorporated if it was felt by the facilitating group that they significantly improved or clarified a statement.

There were three rounds for participants to comment on the developing statements. For each round only statements that had been altered from the previous round were considered. For altered statements, participants received all the comments on the statement and explanation as to why the statement had been changed.

After Round 3, the statements were presented and discussed at the annual Neonatal Screening Working Group meeting (European CF Conference, Brest 2009).

3. Results

3.1. Literature review

The quantity and quality of published trials on the early management of infants with CF were considered poor. Most interventions were graded as D (evidence from published case reports/series or expert opinion). Even when the level of evidence was graded as 1+ with well conducted systematic reviews (for example; anti-staphylococcal prophylaxis and physiotherapy in the asymptomatic child), these were not able to provide clear guidance on management.

3.2. The modified Delphi process

The core group developed 41 statements, which were used in Round One of the modified Delphi process (Fig. 1). Eighty-six CF specialists from Europe and Australia contributed to the modified Delphi process. Consensus was not achieved on five statements, which were modified in light of comments and suggestions. Four new statements were added to reflect specific comments. Fifteen statements were adjusted, despite achieving consensus, as the facilitating group felt this improved the quality of the statement. After the second round, five statements remained to achieve consensus, but alterations for Round 3 enabled consensus to be achieved on four of these outstanding statements. One statement

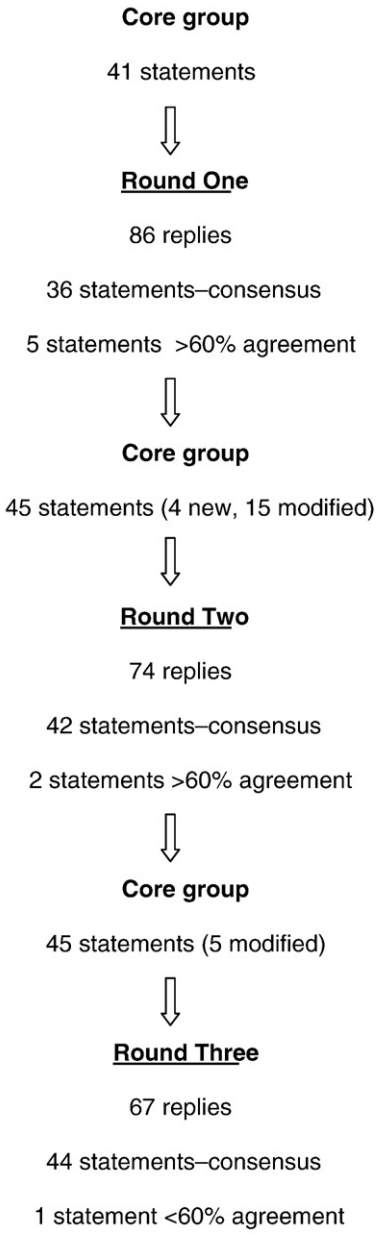

Fig. 1. The stages and outcomes of the modified Delphi method.

failed to reach consensus (see below) despite a number of reiterations.

3.3. General statements

Several statements were modified to strengthen the importance of their content by changing "should" to "must" following analysis of respondents' comments and in line with other ECFS consensus documents (Table 1). This was well received in Round Two with higher levels of consensus achieved. Clarification that the multidisciplinary team must be paediatric followed comments that in some countries the team would not automatically be the case. Given the young age of patients diagnosed through screening this was considered to be essential.

Statements describing the composition of the multidisciplinary team, available resources and prevention of cross-infection were well received with agreement of over 95% in Round One. Follow up of the family with access to genetic counselling, education of families, sweat testing of siblings and communication with primary care achieved consensus levels between 87 and 100%.

A number of participants were concerned about a suggested basic frequency of multidisciplinary review of 6–8 weeks. This statement (number 6) was approaching consensus at 77%. After changing the statement to every 4–8 weeks, 88% agreement was achieved in Round 2.

A statement on accessibility of care was added in response to comments from Round One. The initial statement suggested that families should be able to contact the team at any time. This provoked significant discussion but was approaching consensus (74%). Local clinic resources and service structure obviously determine the availability of the CF team particularly for out of hours care. Modifying the statement to consider these factors, consensus improved to 97% (Statement 9).

Statements concerning guidance on immunisations achieved high levels of agreement (10, 37 and 38). These statements should be read in conjunction with the ECFS Vaccination Group document "Immunisation in the current management of cystic fibrosis patients" [13].

Table 1
General statements.

1	Infants must receive care from a paediatric multidisciplinary team of CF specialists (physician, nurse specialist, physiotherapist, dietician, psychologist, and social worker).
2	Families should be offered access to genetic advice and counselling.
3	Siblings should be sweat-tested.
4	Infants should receive care in a centre with appropriate equipment and resources to facilitate a level of care according to the guidelines.
5	Measures must be in place to prevent cross-infection.
6	Infants must be reviewed in clinic by the team every 4–8 weeks, and more frequently after diagnosis or if there are any clinical concerns.
7	The CF team should communicate clearly and promptly with the primary care team.
8	Education of the families must be implemented from diagnosis. Families should have access to information so that they develop progressively a clear understanding of CF care and what changes to expect as their child grows.
9	Families should be able to contact the CF team during normal working hours. Specific arrangements should be in place for emergencies outside working hours.
10	Parents should be encouraged to ensure their infant receives standard childhood immunisations, according to national guidelines (see also statements 37 and 38).

3.4. Nutritional management

The requirement for baseline nutritional assessment, together with the content and timing of this provoked considerable discussion (Table 2). Significant differences in local practice exist. Some centres perform baseline assessment at first annual review, some centres at diagnosis. The facilitating group considered this a key statement; however we were unable to obtain consensus even following three adaptations of the statement reflecting comments. In fact, levels of agreement

Table 2
Statements on nutritional management.

	Monitoring nutrition and growth
11	Weight, length, and head-circumference should be measured at each consultation and recorded on a growth chart with age specific percentiles.
12	Growth targets should reflect genetic potential, sibling height and local population demographics.
13	At diagnosis, infants must have pancreatic function assessed clinically and by measuring stool fecal elastase. Repeated assessment of pancreatic status is essential during the first year of life if elastase is normal at diagnosis.
	Preventive nutritional care
14	Breast feeding should be encouraged.
15	All infants with pancreatic insufficiency (PI) should be commenced on pancreatic enzyme replacement therapy (PERT). Starting dose should be in the region of 2000 IU lipase per 100 ml standard formula and then increased if there are signs and/or symptoms of malabsorption or an inadequate rate of weight gain.
16	Families of breast-fed infants should receive specific advice regarding PERT, salt supplements and nutritional intake.
17	Infants that receive high doses of PERT (greater than 10 000 IU kg^{-1} day^{-1} lipase) should be reviewed by an experienced CF dietician and/or a Paediatric Gastroenterologist with experience in CF.
18	There is no evidence to support the routine use of therapies to reduce gastric pH in infants.
19	Energy intake should be adapted to achieve normal growth. Higher intake (up to 150% of the dietary reference values for age) may be necessary.
20	There is no evidence to support the routine use of hydrolysed formula, however, it may be of value for infants with non-CF malabsorption (short bowel syndrome, post-infectious lactase deficiency, cholestatic liver disease, and cow's milk protein intolerance).
21	Sodium chloride supplementation (2 mmol kg^{-1} day^{-1}) should be considered for all CF infants, and increased during periods of hot weather and with other causes of high salt loss (for example, diarrhoea, fever and ileostomy).
22	There is no evidence supporting oral supplementation of trace elements beyond the age-appropriate recommended daily allowance.
23	Fat-soluble vitamins need to be supplemented routinely (Appendix A) in infants with pancreatic insufficiency.
24	There is no agreement on the dose and preparation for Vitamin K supplementation. (Appendix A)
	Reactive nutritional care
25	In infants with nutritional concern, dietetic review is essential. It should prompt advice to increase calorie intake, review of PERT, and possibly interventions to reduce gastric acidity.
26	If poor weight gain persists despite optimal PERT, other causes of poor growth/malabsorption should be excluded.

deteriorated with each revision (Appendix C). It was apparent at an open meeting of the ECFS Neonatal Screening Working Group (31st European CF conference, 2009) that disparate views precluded consensus being achieved on this statement.

There was a good level of agreement with the statement that encouraged breast feeding, consistent with WHO recommendations and the ECFS nutrition consensus (Statement 14, 92% agreement). These families require specific advice regarding pancreatic replacement therapy (PERT), sodium supplementation and nutritional intake (Statement 16, 92% agreement). Routine use of hydrolysed formula was not supported except in infants who have malabsorption not directly related to CF (Statement 20, 98% agreement).

In northern Europe 95% of infants are pancreatic insufficient (PI) by 1 year of age [14]. However a significant number of screened infants may be pancreatic sufficient (PS) at diagnosis [15]. Whilst there is a lack of clear data the implication is that a proportion of PS infants will become PI over the course of the first year of life. In support of this, a study of NBS CF infants in Northern Italy and Sydney, Australia, demonstrated 80/315 infants to be PS shortly after diagnosis. Twenty of these PS infants then became PI over a median of 12 months (determined through clinical features, fecal fat measurement and pancreatic stimulation tests) [16]. Statement 13 advises initial assessment of pancreatic function and then repeated assessment if fecal elastase is within the normal range at diagnosis (83% agreement).

Calculating the dose of PERT in infants can be complex, there is a lack of evidence examining the co-efficient of fat absorption in this age group and dosing will depend on residual pancreatic function which will vary between infants and may alter over time in an individual infant [15]. These differences are reflected in the variety of practice across Europe and the number of suggestions and comments on Statement 15. This statement had particularly useful input from senior dietitians. Best agreement (91%) was achieved in Round Three when a minimum starting dose was suggested rather than a dosing range. It should be highlighted that this is a minimum starting dose and there must be a low threshold for increasing doses according to inadequate rate of weight gain or evidence of malabsorption. Other factors affecting weight gain and malabsorption should also be considered (see Statements 25 and 26). The dosage should be adjusted for practical purposes according to PERT preparation used.

Statement 15 refers to those infants receiving standard infant formula; infants receiving breast milk should have individually tailored advice regarding PERT and supplementation (Statement 16).

Infants on high doses of PERT need thorough review and assessment (Statement 17). The initial statement, suggesting involvement of a paediatric gastroenterologist failed to reach consensus (67%). Regional practice varies but most respondents felt strongly that the assessment was more appropriately performed by experienced CF dietitian with the addition of a paediatric gastroenterologist where necessary (85% agreement).

There appears to be considerable variation in practice with respect to salt supplementation. The original statement suggested routine supplementation in all infants and failed to reach consensus at 61% agreement. Changing the statement to "consideration to sodium supplementation should be given in all infants particularly in situations of increased salt loss" improved the agreement and consensus was achieved (Statement 21, 91% agreement). Situations that might result in increased salt loss are a warm climate and periods of ill health. Specific advice should be given for breast feeding infants (Statement 16).

Table 3
Statements on pulmonary disease management.

	Monitoring pulmonary status
27	Infants should have a detailed clinical respiratory assessment at each clinic visit (Appendix B).
28	Evidence of respiratory infection (cough, wheeze, increased work of breathing, and added sounds on auscultation) must prompt respiratory culture and additional antibiotic treatment.
29	Respiratory cultures should be performed at each visit, according to best local practice.
30	Chest radiograph should be performed at baseline assessment following diagnosis and if clinically indicated (persisting symptoms despite treatment).
31	There is insufficient evidence to support routine High Resolution Computed Tomography (HRCT) in the first year of life.
32	There is insufficient evidence to support routine Infant Pulmonary Function Tests.
33	Bronchoalveolar lavage (flexible bronchoscopy) should be considered in symptomatic infants not responding to standard therapies if routine cultures are non-contributive.
34	If the infant remains symptomatic with persistently negative respiratory cultures, other causes, especially Gastro-Oesophageal Reflux, should be excluded.
35	Measuring *Pseudomonas* antibody levels may identify early airway infection, but there is insufficient evidence and standardization of assays to support routine testing in the first year of life.
	Preventive pulmonary care
36	Techniques to facilitate airway clearance should be undertaken on a regular basis. Debate exists as to the best strategy in asymptomatic infants.
37	Anti-influenza vaccination should be given after the age of 6 months (2 injections of 0.25 ml at 1 month interval)
38	RSV infection is considered an important factor in CF lung disease; however at present there is insufficient evidence to support the routine use of passive immunisation in the first year of life.
39	There is insufficient evidence to support the routine use of anti-pseudomonal vaccination at present.
40	Anti-staphylococcal antibiotic prophylaxis may be indicated as it reduces isolation of *Staphylococcus aureus* from respiratory cultures in the first year of life but longer term clinical outcomes are not clear. This is an area of debate, as studies have suggested a possible association between the use of cefalexin and increased *Pseudomonas aeruginosa* infection.
	Reactive respiratory care
41	Physiotherapy for airway clearance should be undertaken more frequently in the symptomatic infant
42	Antibiotic treatment must be initiated following recognition of *Pseudomonas aeruginosa*, even in the asymptomatic infant. For other pathogens, there is less clear agreement and treatment should be guided by local policies.
43	For *Pseudomonas aeruginosa*, this should be a protocol aimed at eradication.
44	Intravenous antibiotics should be considered if the infant remains symptomatic despite initial therapy or if respiratory cultures remain positive.

3.5. Pulmonary disease management

Overall there were much better levels of agreement for statements on pulmonary care (Table 3). Debate exists as to the best strategy for airway clearance in infants, however Statement 36 recommended that this should be undertaken regularly (regardless of technique) and achieved a good level of agreement (88%).

The influenza vaccine was strongly supported (Statement 37, 96% agreement). There was also agreement that there was insufficient evidence to support either passive RSV immunisation or anti-pseudomonal vaccines (Statements 38 and 39).

A significant area of debate was the use of routine measurement of *Pseudomonas* antibodies to identify early airway infection. The first suggestion was adapted to include some recognition of the potential of this test, but reflected that insufficient evidence and difficulties with standardization of assays did not support routine testing in this age group. With these changes a good level of agreement was achieved in Round Two (Statement 36, 90% agreement).

Some statements achieved adequate levels of agreement in Round One but were adapted in Round Two to reflect comments. For example, the Statement 40 regarding anti-staphylococcal prophylaxis was made more informative and this improved the level of agreement from 84% to 89%.

There was some disagreement with regard to antibiotic treatment for the asymptomatic infant with a positive respiratory culture. When this was specified as *Pseudomonas aeruginosa*, levels of agreement improved (Statement 42, 91% agreement). For other pathogens there is less clear agreement and teams were advised to follow local policies.

4. Discussion

This process has resulted in 44 statements that guide the early management of screened infants with CF. Over 86 CF specialists from 19 different countries have contributed to these statements through the modified Delphi methodology. Participants represented a number of disciplines including dietetics, physiotherapy, genetics, nursing and medicine. Over the course of the three rounds of consensus development, 660 comments were generated by the participants and assessed by the facilitating group. Statements developed by the core group were adjusted and improved significantly through this process.

Good levels of agreement were achieved for all statements except one, which did not achieve consensus despite numerous reiterations. This statement examined the need for, timing and content of a baseline nutritional assessment. Arguments against a baseline assessment included a perceived lack of useful additional information and the potential of distress for the infant and family (if blood tests are involved). Arguments in favour of baseline assessment are the early recognition of nutritional deficiencies and electrolyte imbalance. A number of changes to the statement were made reflecting comments received; however this resulted in a reduction in agreement (Appendix C). Lack of agreement on this issue was further illustrated by an open discussion at the 2009 ECFC workshop on newborn screening. There is good agreement on the need for some form of baseline assessment; the lack of consensus reflects both the variability in local practice and strength of conviction of individuals on this topic. We recommend therefore that CF teams discuss these issues and reflect on their local practice. Further research is needed to determine the most appropriate strategy for monitoring nutritional progress in this cohort.

As newborn screening for CF becomes established across most of Europe, these statements will guide early management. This process has highlighted the urgent need for large randomised controlled trials of interventions in this screened population (Table 4). All infants with CF identified through NBS should have opportunity to be included in such a study. This process will be repeated in 2011 to ensure new sources of evidence are incorporated into the guidelines.

Table 4
Interventions that require clinical studies in infants with CF diagnosed following newborn screening.

Intervention	Current status of clinical trials
Salt supplementation	None known
Vitamin K for bone disease	None known
Palivizumab to prevent RSV infection in the first year of life	Systematic review to be published soon.
Long-term ursodeoxycholic acid to prevent CF liver disease	None known
Early versus late pancreatic enzyme replacement therapy	None known
HRCT to detect lung disease in early infancy	Perth/Melbourne study nearing completion
Regular flexible bronchoscopy in early infancy	Sydney/Brisbane study nearing completion
Regular infant pulmonary function tests	London study recruiting
Anti-staphylococcal prophylaxis	None known
Airway clearance techniques in infants	None known
Anti-pseudomonal immunisation	Results of phase 3 studies awaited

Cystic Fibrosis Specialists who contributed to the consensus:

Arets Bert	Wilhelmina Children's Hospital, Utrecht, Netherlands
Ballman Manfred*	Medical School Hannover, Germany
Ball Rosemary	St James University Hospital, Leeds, United Kingdom
Barben Jürg	Children's Hospital, St Gallen, Switzerland
Bellon Gabriel	Hôpital Debrousse, Lyon, France
Benden Christian	University Hospital Zurich, Switzerland
Blaikie Lesley	Raigmore Hospital, NHS Highland Trust, Scotland, United Kingdom
Brownlee Keith	St James University Hospital, Leeds, United Kingdom
Bryon Mandy	Great Ormond Street Hospital, London, United Kingdom
Burrows Elinor	Royal Liverpool Children's Hospital, Liverpool, United Kingdom
Bush Andrew	Royal Brompton Hospital, London, United Kingdom
Castellani Carlo	Cystic Fibrosis Center, Azienda Ospedaliera Verona, Verona, Italy
Conway Steven	St James Hospital University Hospital, Leeds, United Kingdom
Corbetta Carlo	Laboratorio di Riferimento regionale, Ospedale dei Bambini, Milano, Italy

(*continued on next page*)

(*continued*)

Cystic Fibrosis Specialists who contributed to the consensus:	
Dankert-Roelse Jeanette	Atrium Medisch Centrum Parkstad, Heerlen, Netherlands
De Boeck Kristiane	University Hospital Gasthuisberg, Leuven, Belgium
Derichs Nico	Cystic Fibrosis Center, Medizinische Hochschule, Hannover, Germany
Desai Maya	Birmingham Children's Hospital, Birmingham, United Kingdom
Dodge John	University of Wales, Swansea, United Kingdom
Doull Iollo	Children's Hospital for Wales, Cardiff, United Kingdom
Dubus Jean-Christophe	Unité de Médecine Infantile & CRCM Pédiatrique, CHU Timone-Enfants, Marseille, France
Duiverman Eric J	Beatrix Children's Hospital/University Medical Center Groningen, Netherlands
Ellemunter Helmut	Cystic Fibrosis Center Innsbruck, Innsbruck Medical University, Austria
Ellison Julie	Mid Cheshire NHS Trust, United Kingdom
Farrell Phillip*	University of Wisconsin, USA
Feilcke Maria	Munich Cystic Fibrosis Centre, Germany
Foote Keith	Royal Hampshire County Hospital, United Kingdom
Gartner Silvia	Hospital Universitario Materno Infantil Vall d'Hebron, Barcelona, Spain
Gursli Sandra	Norwegian National Center for CF, Ulleval University Hospital, Kirkev, Norway
Hammermann Jutta*	Dresden Cystic Fibrosis Centre, Germany
Hatziagorou Elpis	Cystic Fibrosis Unit, Aristotle University of Thessaloniki, Greece
Havermans Trudy	UZ Leuven, Belgium
Hendriks JJE	MUMC, Maastricht, Netherlands
Høiby Niels	Rigshospitalet, University of Copenhagen, Denmark
Kashirskaya Nataliya	Research Centre for Medical Genetics, Moscow, Russia
Kavanagh Caroline	Norfolk and Norwich University Hospital, United Kingdom
Kollberg Hans	Former director of Uppsala CF-center Sweden
Lannefors Louise	Lund CF-centre, Lund University Hospital, Sweden
Lebecque Patrick	Cliniques Universitaires St Luc - UCL, Bruxelles, Belgium
Lenoir Gérard	Necker-Enfants Malades Hospital, Paris, France
Littlewood Jim M	Chairman Cystic Fibrosis Trust, United Kingdom
Lucidi Vincenzina	Bambino gesù hospital, Roma, Italy
Malfroot Anne	Universitar Zeikenhuis Brussel, Belgium
Maretti Tanja	University Pediatric Clinic in Skopje, R. Macedonia
Marguet Christophe	CHU-Rouen Hôpital Charles Nicolle, Rouen, France
McCabe Helen	Newcastle Upon Tyne Hospitals, United Kingdom
Mehta Anil	University of Dundee, Scotland, United Kingdom
Moeller Alexander	University Children's Hospital, Zurich, Switzerland
Munck Anne	AFDPHE, Paris, France
Nährlich Lutz	Universitätsklinikum Erlangen, Germany
Nilsson Mikael	Lund CF-centre, Lund University Hospital, Sweden
Nixon Wendy	Birmingham Children's Hospital, Birmingham, United Kingdom
Norek Aleksandra	Department of Medical Genetics, Institute of Mother and Child, Warsaw, Poland
Padoan Rita	Cystic Fibrosis Service, Spedali Civili Brescia, Italy
Pollitt Rodney	Sheffield Children's Hospital, Sheffield, United Kingdom
Prasad Ammani	Great Ormond Street Hospital, London, United Kingdom
Proesmans Marijke	University Hospital Leuven, Belgium
Rault Gilles	CF Center, Roscoff, Nantes University Hospital, France
Reid Alastair	Royal Belfast Hospital for Sick Children, United Kingdom
Reimann Andreas	Chief Executive Officer, Mukoviszidose e.V, Germany
Renner Sabine	Medical University Vienna, Austria
Repetto Teresa	CF Center Meyer Hospital, Florence, Italy
Robberecht Eddy	Director CF Centre Ghent University Hospital, Ghent, Belgium
Roussey Michel	Hopital Sud, Rennes and AFDPHE, Paris, France
Sammon Alec	Lay representative, France
Sands Dorota*	CF Center, Institute of Mother and Child, Warsaw, Poland
Schuster Anje	University of Duesseldorf, Germany
Schwarz Martin J	Regional Molecular Genetics Service, St Mary's Hospital, Manchester
Sermet-Gaudelus Isabelle*	CRCM, Hopital Necker-Enfants Malades, Paris, France
Shankar Anu	University Hospital Lewisham, London, United Kingdom
Skalicka Veronika	CF Centre Prague, University Hospital Motol, Praha, Czech Republic
Smyth Alan	University of Nottingham, United Kingdom
Sommerburg Olaf	Heidelberg Cystic Fibrosis Centre, Germany
Southern Kevin*	University of Liverpool, United Kingdom
Staab Doris	CF Centre Berlin, Germany
Storrosten Olav	Ullevl University Hospital, Oslo, Norway
Stuhrmann Manfred	Institute of Human Genetics, Hannover Medical School, Germany
Taccetti Giovanni	CF Center Meyer Hospital, Florence, Italy
Taylor Chris	Sheffield Children's NHS Foundation Trust, United Kingdom
Tješić-Drinković Dorian	University Hospital Center Zagreb, Zagreb, Croatia
Torresani Toni	University Children's Hospital, Zurich, Switzerland
Tsanakas John	Cystic Fibrosis Unit, Aristotle University of Thessaloniki, Greece
Van Steenbergen Marianne	Den Bosch, Netherlands
Vavrova Vera	CF Centre Prague, University Hospital Motol, Czech Republic
Vernooij Annette*	National Institute of Public Health, Bilthoven Netherlands
Watling Ruth	Royal Liverpool Children's Hospital, United Kingdom
Wilschanski Michael	Hadassah University Hospital, Jerusalem, Israel
Wilcken Bridget	Westmead Children's Hospital, New South Wales, Australia
Wyatt Hilary	Kings College Hospital, London, United Kingdom

*Members of the core group.

Acknowledgements

We would like to thank the support of the ECFS. We are grateful to Dr Jean Craig, who has continued to provide advice regarding the Delphi methodology.

Appendix A

Suggested daily doses for fat-soluble vitamins in infants less than 1 year

Vitamin A 1500 IU
Vitamin E 40–50 IU
Vitamin D 400–800 IU

Vitamin K a dose for Vitamin K supplementation in cystic fibrosis is not established. Recommendations for infants range from 0.3 to 1 mg daily dose [17].

Appendix B

Respiratory assessment

a) History:
   – new or increased cough
   – new or increased wheeze
   – poor feeding
   – fever
   – increased respiratory rate/breathlessness
b) Examination:
   – respiratory rate
   – use of accessory muscles/dyspnoea
   – cough/wheeze/hyperinflation
   – wheeze and/or crackles on auscultation
c) Pulse oximetry
d) Physiotherapy assessment

Appendix C

Statement examining baseline assessment — alterations and levels of agreement

Round One (77% agreement)

After diagnosis, a baseline assessment is done that includes, as a minimum, the following tests:

- Plasma fat-soluble vitamin levels
- Serum albumin.
- Serum liver function tests
- Serum and urine sodium.
- Full blood count and iron status.

These measurements must be repeated every year (more frequently if clinical concern).

Round Two (74% agreement)

Within 3 months after diagnosis, a baseline assessment must be done, that includes, as a minimum:

- Plasma fat-soluble vitamin levels
- Serum albumin and liver function tests
- Serum and urine sodium
- Full blood count

Round Three (68% agreement)

A baseline assessment should be performed according to local practice; there is debate as to the timing and content of this assessment.

References

[1] Castellani C, Southern KW, Brownlee K, Dankert Roelse J, Duff A, Farrell M, et al. European best practice guidelines for cystic fibrosis neonatal screening. J Cyst Fibros May, 2009;8(3):153–73.
[2] Southern KW, Merelle MM, Dankert-Roelse JE, Nagelkerke AD. Newborn screening for cystic fibrosis. Cochrane database of systematic reviews (Online). 2009(1):CD001402.
[3] Southern KW, Munck A, Pollitt R, Travert G, Zanolla L, Dankert-Roelse J, et al. A survey of newborn screening for cystic fibrosis in Europe. J Cyst Fibros Jan 2007;6(1):57–65.
[4] Doull IJ, Ryley HC, Weller P, Goodchild MC. Cystic fibrosis-related deaths in infancy and the effect of newborn screening. Pediatr Pulmonol May 2001;31(5):363–6.
[5] Farrell PM, Kosorok MR, Laxova A, Shen G, Koscik RE, Bruns WT, et al. Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. New Eng j med Oct 2 1997;337(14):963–9.
[6] Grosse SD, Rosenfeld M, Devine OJ, Lai HJ, Farrell PM. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. J Pediatr Sep 2006;149(3):362–6.
[7] Koscik RL, Lai HJ, Laxova A, Zaremba KM, Kosorok MR, Douglas JA, et al. Preventing early, prolonged vitamin E deficiency: an opportunity for better cognitive outcomes via early diagnosis through neonatal screening. J Pediatr Sep 2005;147(3 Suppl):S51–6.
[8] Sims EJ, Clark A, McCormick J, Mehta G, Connett G, Mehta A. Cystic fibrosis diagnosed after 2 months of age leads to worse outcomes and requires more therapy. Pediatrics Jan 2007;119(1):19–28.
[9] Farrell PM. Is newborn screening for cystic fibrosis a basic human right? J Cyst Fibros May 2008;7(3):262–5.
[10] Mayell SJ, Munck A, Craig JV, Sermet I, Brownlee KG, Schwarz MJ, et al. A European consensus for the evaluation and management of infants with an equivocal diagnosis following newborn screening for cystic fibrosis. J Cyst Fibros Jan 2009;8(1):71–8.
[11] Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ Aug 11 2001;323(7308):334–6 Clinical research ed.
[12] Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, Askham J, et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess (Winchester, England) 1998;2(3):1–88 I–iv.
[13] Malfroot A, Adam G, Ciofu O, Doring G, Knoop C, Lang AB, et al. Immunisation in the current management of cystic fibrosis patients. J Cyst Fibros May 2005;4(2):77–87.
[14] Littlewood JM, Wolfe SP, Conway SP. Diagnosis and treatment of intestinal malabsorption in cystic fibrosis. Pediatr Pulmonol Jan 2006;41 (1):35–49.
[15] 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 Apr 1992;120(4 Pt 1):533–40.
[16] Cipolli M, Castellani C, Wilcken B, Massie J, McKay K, Gruca M, et al. Pancreatic phenotype in infants with cystic fibrosis identified by mutation screening. Arch Dis Child Oct 2007;92(10):842–6.
[17] 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 Jun 2002;1(2):51–75.