Review

European Journal of
Pediatrics

Eur J Pediatr (1990) 149:742–751

Cystic fibrosis, pathophysiological and clinical aspects*

H. J. Neijens[1], M. Sinaasappel[1], R. de Groot[1], J. C. de Jongste[1], and S. E. Overbeek[2]

[1]Department of Paediatrics, Ersasmus University and University Hospital Rotterdam/Sophia Children's Hospital, Gordelweg 160, 3038 GE Rotterdam, The Netherlands
[2]Department of Respiratory Diseases, University Hospital Rotterdam/Dijkzigt Hospital, Dr. Molewaterplein 40, Rotterdam, The Netherlands

Received November 30, 1989 / Accepted April 22, 1990

Abstract. Cystic fibrosis is a lethal, hereditary, until recently little understood disease, which leads to progressive functional disturbances in various organs, including the lungs, liver and pancreas. Knowledge of the genetic and cellular abnormalities is rapidly progressing, but therapy is still symptomatic and based on insufficiently controlled and short-term studies. At present the therapeutic approach aims to combat respiratory infections by optimal antibiotic therapy, combined with techniques to promote sputum evacuation. Additional measures attempt to optimise both nutritional state and physical condition. Median survival has imporved from approximately 1 year to about 25 years during the past 3 decades. This article summarises present information on disease mechanisms and treatment.

Key words: Cystic fibrosis – Pathophysiology – Respiratory aspects – Gastro-intestinal aspects – Hepatic aspects

Introduction

Cystic fibrosis (CF) was first described in the 1930s [3, 20], and was only clearly defined in the mid 1950s with the development of the sweat test [81]. The fundamental defect in CF appears to be a dysfunction of epithelial cells leading to abnormal secretions which cause obstruction of organ ducts [82]. CF involves a variety of organs, particularly the lungs and abdominal organs. The manifestations and severity of CF vary considerably between patients, a feature that has not yet been satisfactorily explained. CF is found in all ethnic groups, but most frequently amongst Caucasians. High incidences have been reported in Europe, as well as in areas populated by emigrants from European countries, such as North America and Australia. The prevalence in Europe is around 1:3000 and varies between 1:500 (Scotland) and 1:15,000 (Italy). CF is the most common lethal, autosomal recessive disorder among Caucasians.

The abnormal gene has recently been cloned and the biochemistry of the cellular defect largely unravelled. New information on molecular genetics and cellular physiology, as described in the first of two review articles on CF [36], provides a better understanding of the pathophysiology and may lead to new therapeutic approaches.

This second article will discuss current opinion about respiratory, gastrointestinal and hepatic function in CF.

* This is the second of two articles on cystic fibrosis, the first of which appeared in the previous issue of this journal, vol. 149, pp. 670–677 (1990)

Offprint requests to: H. J. Neijens

Abbreviations: ABPA = allergic bronchopulmonary aspergillosis; CF = cystic fibrosis; DIOS = distal intestinal obstruction syndrome; EFA = essential fatty acids; FEV_1 = forced expiratory volume in Is; MI = meconium ileus

Pathophysiology of respiratory abnormalities

The pulmonary infections in CF are unique because of the underlying disorder, the host defence factors involved, the role of certain bacterial species, and the chronicity of infection, with potential for immunopathological damage.

A vicious circle operates in CF between mucous plugging of the airways, infection and inflammation. The underlying cause is probably a defective regulation of the chloride channel, which is located in the apical membrane of the epithelial cells [7, 36]. This results in desiccation of secretions, increase in the viscosity of mucus and a decrease in mucociliary clearance. Exaggerated inflammatory processes are usually found in CF patients and host defence factors seem to play a role in tissue damage.

The level of serum IgG is related to the disease state [122]. Early in the course of the disease, serum IgG levels are relatively low. With progression of the disease, IgG concentrations usually rise to high values which may lead to immune-complex formation [123]. Immune-complexes activate granulocytes and macrophages, resulting in the release of a variety of mediators. The presence of immune-complexes and granulocyte elastase in bron-

chial secretions [107] and plasma [41], and the amount of urinary collagen metabolites [2] correlate with a poor clinical condition. High levels of enzymes such as elastase and myeloperoxidase may be responsible for the destruction of pulmonary tissue [34]. Immune-complexes (possibly together with other mechanisms) are thought to be responsible for extra-pulmonary manifestations in CF such as arthritis and vasculitis.

Bacterial factors may further modify tissue and immune responses. A remarkable characteristic of the strains of *Pseudomonas aeruginosa* colonising CF patients is the production of a mucoid exopolysaccharide which increases adherence to the respiratory tract and which has an anti-phagocytic effect [76]. Suppression of phagocytosis by both polymorphonuclear leucocytes and alveolar macrophages by exopolysaccharide [80, 88] and by exotoxin A [77, 121] has been reported. Other products of *P. aeruginosa,* such as elastase and other proteases, might also compromise host defences or lead to tissue destruction [24, 46].

Thus, both specific and non-specific host immune responses seem to contribute to pulmonary disease [108].

The bacterial species involved in the early phase of the disease are usually *Staphylococcus aureus* and, sometimes, *Haemophilus influenzae.* The explanation for the preference for *S. aureus* is unknown. It has been suggested that infection with *S. aureus* induces chronic lung disease and predisposes to *Pseudomonas* infections, but this remains to be proven. The detection of *H. influenzae* may be difficult due to overgrowth of other micro-organisms.

Pseudomonas infections are increasingly important in advancing disease. With age, colonisation becomes more prevalent and exacerbations tend to become more frequent [17]. *P. aeruginosa* once present, is virtually impossible to eradicate.

Respiratory tract colonisation with *P. cepacia,* a highly resistent strain, has increased in several CF centres. It has been associated with shortened survival [112].

Some micro-organisms, such as respiratory viruses, *Chlamydia* and *Mycoplasma,* are reported to be associated with pulmonary exacerbations [39]. Peterson et al. [75] observed *respiratory syncytical virus* relatively often in relation with exacerbations in patients colonised with *P. aeruginosa* [1]. This suggests a synergistic relationship between virus and bacteria, possibly explained by depression of host defence induced by the virus [28].

Assessment of bronchial inflammation

Symptoms of an infectious exacerbation include increased coughing and an increase in the amount, purulence and viscosity of sputum, as well as in dyspnoea, particularly after exercise. Malaise, decrease in appetite and loss of weight nearly always accompany respiratory exacerbations. Fever or leukocytosis are only occasionally present.

Culture of sputum identifies the causative micro-organisms, and quantitative cultures may be helpful in assessing the severity of infections [111]. A recent development is the application of DNA probes to identify micro-organisms [116]. The major advantages of this technique are specificity, the absence of interference by prior antibiotic therapy, and the possibility of identifying bacteria in mixed cultures. The application of radioactive labels for DNA probes hampers its routine use; nonradioactive labeling methods are being developed.

The extent of the inflammatory process is reflected by radiological abnormalities and by lung function. The most reliable means of detecting exacerbations are a decrease in the forced expiratory volume in 1 s (FEV_1) and the forced vital capacity. In mild, or intermediate severity, the radiological abnormalities usually correlate with pulmonary function. In advanced disease this correlation is usually poor, because at this stage radiological abnormalities are so severe that further changes are barely detectable and lung function becomes a better guide to assess the severeity of the lung process.

The most widely used scoring system is that described by Shwachman and Kulczyski [89] in which four aspects are assessed: activity, physical examination, nutrition and the chest roentgenogram, but this system does not include lung function results.

Treatment of respiratory infections

General considerations

Antimicrobial therapy for CF has largely developed empirically. Uncertainty remains concerning the indications for treatment, the benefits of prophylactic administration of antibiotics, the kinds of drugs to use [31], and the optimal dosage and duration of treatment.

The aims of treatment are to reduce the severity and duration of the exacerbations, to prolong exacerbation-free periods and to minimise lung damage.

Criteria which may be used to monitor the effectiveness of treatment are a reduction in the volume and purulence of sputum, an improvement in lung function and an increase in body weight. The return of FEV_1 and weight to pre-exacerbation values are good indicators of recovery.

The optimal duration of therapy is still uncertain. Weekly pulmonary function tests and assessment of other indicators are useful in determining improvement. We find that 2–3 weeks of treatment are often necessary, particularly for severe infections.

The clinical efficacy of a particular antibiotic may be different from the potency in in-vitro tests. This discrepancy may be explained by mixed bacterial populations of susceptible and resistant strains, by variation in penetration and by local interactions with cells and proteins [62], as antibiotic activity can be antagonised by factors in sputum [78]. Thus, although in-vitro measurements are important in the choice of antibiotics, treatment must be guided by an evaluation of the clinical response. The pharmacokinetics of many antibiotics are different in CF patients, and relatively low serum and sputum levels (especially of aminoglycosides [42, 56] and ureidopenicillins) are often found. This is caused by an increase

Table 1. Antibiotic treatment in the case of an infectious exacerbation

Choice		Antibiotic	Dose (mg/kg/24 h)	Gifts per 24 h	Guideline
Staphylococci					
Oral	1.	(Flu)cloxacillin	50–100	4	
	2.	Erythromycin	50	4	
i.v.	1.	(Flu)cloxacillin	150	4	
	2.	Erythromycin	50–100	3	
	3.	Vancomycin	50–100	4	control serum level
Heamophilus Influenzae					
Oral	1.	Amoxicillin Amoxicillin and clavulanic acid (if lactamase +)	50 i.v. 100–150	4	
	2.	Cotrimoxazole	6/30	3	
	3.	Cephalosporin (Cefuroxime)	30 i.v. 100–150	2	
Pseudomonas					
Oral	1.	Ciprofloxacin	30	3	
Inhalation	1.	Aminoglycoside			
		Tobramycin	80 mg each inhal.	2–3	
	2.	± Ureidopenicillin	5000 mg each inhal.		
i.v.	1.	Aminoglycoside			adjust: serum peak
		Tobramicine	10	3	8–10, though 1–2 mg/l
		or Amikacin	30	3	adjust: serum peak 25–30, trough < 5 mg/l
		Combined with: Ticarcillin/Azlocillin	450	4 or continuous infusion	
		or combined with: Ceftazidime	300	4	
		Cefsulodine	200	or continuous infusion	
	2.	Ceftazidime	300	4	
	3.	Imipenem	100	4	

in total body clearance or a relatively large volume of distribution [35]. Measurement of serum levels, especially for aminoglycosides, is important to ensure that therapeutic, but non-toxic concentrations are achieved.

The usually strategy in therapy is to prescribe antibiotics once an exacerbation is detected. Alternatively prophylactic therapy, using continuous or intermittent antibiotics on a regular basis, may be applied. Prophylactic therapy in preventing staphylococcal colonisation has not been sufficiently studied to determine its value [40, 86, 110].

Prophylaxis against *Pseudomonas* with aminoglycosides or ceftazidime sprays is currently under study. On a short-term basis this seems to be effective [12, 85], but long-term studies are needed. Oral anti-pseudomonal antibiotics, the quinolones, recently became available. Their benefit on a long-term basis has to be established.

Whether i.v. antibiotic courses with aminoglycosides or cephalosporins at regular intervals are capable of modifying the course of the disease in the long run, and whether this outweighs the risks and costs of such treatment is still a matter of debate.

The development of bacterial resistance to antibiotics is an increasing problem, especially in patients with advanced disease who require frequent treatment. Antibiotic therapy may lead to selection of pre-existing mutant resistent organisms. Combinations of antibiotics, or periodical changes in regimens may reduce the occurrence of such resistance [9, 21, 50, 92].

Choice of antibiotics (see Table 1)

Alternative choices of antibiotics are given in the Table, listed for the bacteria commonly observed in CF patients.

The various aminoglycosides [38, 58], and the various ureidopenicillins (azlo-, meslo- and piperacillin) [64, 73, 84] do not seem to have clear differences in efficacy. Piperacillin may produce serum-sickness-like symptoms, and these seem to be relatively common in CF patients [104]. Other regimens need to be considered. Firstly, resistance to ureido-penicillin is increasing. Resistance to ticarcillin has increased to 62% in some studies [60], whereas resistance to cephalosporins, such as ceftazidime, is currently appreciably lower [59]. Secondly, aminoglycosides are potentially oto- and nephrotoxic [71]. Relatively high doses and repeated courses gradually increase

the risk of toxic effects. The dose of aminoglycosides should be based on measurements of serum levels [42].

The cephalosporins, ceftazidime and cefsulodin, can be prescribed alone or in combination with tobramycin. Ceftazidime monotherapy has been found to produce similar improvement in respiratory function and clinical conditions to the combination of an ureidopenicillin and an aminoglycoside [10, 70]. Ceftazidime is of particular importance for the treatment of *P. cepacia*. *P. cepacia* is not sensitive to aminoglycosides, but often has a good in-vitro sensitivity to cotrimoxazole, ceftazidime, ciprofloxacin [32, 43], amiloride plus tobramycin [14] and chloramphenicol.

The quinolones, e.g. ciprofloxacin, given orally have been found to have excellent tissue penetration and to be active against *Pseudomonas* [93, 98]. Ciprofoxacin seems to be a major advance because of its efficacy as oral therapy, facilitating home treatment. Side-effects, namely cartilage abnormalities, have been reported in animal studies, but little information about the effects and side-effects in children is available. Resistence has already been found.

Imipenem is effective in the treatment of pulmonary infections in CF patients [49]. However, resistance develops in many patients after a short treatment period [49, 72].

Treatment of CF respiratory disease includes, apart from antibiotics, inhalation and physiotherapy. In general the beneficial effects of physiotherapy have been difficult to demonstrate objectively, but some patients report subjective improvement [48].

Inhalation therapy consists of saline sprays with or without a mucolytic agent and a bronchodilator. Chest physiotherapy attempts to compensate for impaired mucociliary clearance. A number of new techniques have been added to conventional physiotherapy (chest percussion, vibration and compression, together with postural drainage and assisted coughing). Autogenic drainage and the forced expiration technique (both special cough techniques) try to avoid airway compression during expiration by reducing positive expiratory transthoracic pressures [109].

Positive expiratory pressure mask physiotherapy achieves the same goal by expiring against an external airflow resistence (individually adapted between 10–15 cmH_2O) [117]. Physical exercise promotes clearance of the lungs and improves the physical condition of CF patients [69].

The newly developed techniques which need active co-operation of the patient are often difficult to use in very young children and in some older patients, especially those with severe disease. An advantage of these techniques is the improved independence of the patients.

Complications

Major respiratory complications in CF include haemoptysis, pneumothorax, cor pulmonale, and respiratory failure.

Haemoptysis occurs in approximately 5% of CF patients, mostly in those with pronounced pulmonary abnormalities [102]. An infectious exacerbation is often the direct trigger of haemoptysis. Localisation of the site of bleeding is not always easy, although some patients may indicate the region by localising sensations of fullness, gurgling and pain. Arteriography is not often helpful in determining the site of the bleeding. Bronchoscopy is the best method of localising the haemorrhage and allows removal of blood from bronchi and haemostasis either by vasoconstrictive agents or by tamponade. Clinical experience has shown that vasopressin (either as an i.v. bolus, or continuous infusion) may stop the bleeding [55].

Bronchial artery embolization is very successful in preventing recurrence of haemoptysis [23]. Foam gel or other vessel obstructive agents are passed via a catheter into the bronchial arteries supplying the involved lobes. The procedure is relatively safe if the bronchial and spinal arteries are clearly identified in order to avoid blocking of the latter. Many patients experience minor bleeding from mucosal lesions which usually heals rapidly and requires no specific therapy.

Pneumothorax is probably related to the development of subpleural blebs, and airway obstruction by tenacious secretions. Patients present with subacute or acute shortness of breath, chest pain and cyanosis. When spontaneous improvement does not occur or symptoms are severe, pneumothorax should be treated by chest drainage. However a large pneumothorax and/or marked symptoms may require more definitive therapy. A chest drain usually results in the resolution of the pneumothorax, but recurrences can occur. In such cases additional procedures can be considered, including application of chemical agents in the plural cavity or surgical stripping of the parietal pleura. Both methods appear to be equally effective [44, 94, 100, 103]. The use of techniques leading to pleural adhesions should be balanced against the problems of performing lung-transplantation [90] after pleurectomy.

Allergic bronchopulmonary aspergillosis (ABPA) occurs in some CF patients. *Aspergillus fumigatus* colonises many CF patients and induces IgG and IgE antibodies. The Toronto group evaluated a large group of patients for immunological criteria suggestive of ABPA, including positive skin testing for *Aspergillus* [22]. ABPA indicators were found in 10% of their patients, most of whom had advanced disease. The Copenhagen group estimated an ABPA incidence of about 0.9 per 100 CF patients per year [87]. ABPA can be diagnosed if bronchospasm and variable pulmonary infiltrates are found in addition to eosinophilia and the presence of specific IgG and IgE antibodies. The clinical and radiological signs, however, may be difficult to distinguish from the usual symptoms of CF lung disease. The levels of *Aspergillus* IgG antibodies are closely related to pulmonary function [26]. Maguire et al. [57] treated ABPA patients successfully with corticosteroids daily for 1–5 months, followed by a alternate-day scheme for 6 months.

Hypoxaemia becomes more pronounced with progression of lung function abnormalities, with the subsequent development of hypercapnia. This may be asymptomatic for a long time. Hypoxaemia may be accompanied by

symptoms such as morning headache, due to a fall in nocturnal oxygen saturation. Hypoxia may also worsen with exercise in patients with advanced airways disease. A FEV_1 below 60%–65% of the expected value correlates with a risk of hypoxia [119]. Hypoxaemia (O_2 saturation below 85%–90%) can be treated with supplementary oxygen, although its long-term benefit is not clear. Recurrent periods of hypoxia produce or aggravate pulmonary hypertension and cor pulmonale and may be a risk under conditions such as air travel [54]. Clinically manifest cor pulmonale usually indicates a short survival time.

Gastro-intestinal abnormalities

The CF defect affects potentially all abdominal organs with a secretory function [27, 51, 83]. The function of the exocrine pancreas and the intestine is almost always compromised, but liver function is less frequently impaired.

Several studies have shown chloride impermeability of apical membranes of crypt cells in the small intestine and the rectum from CF patients after stimulation with cyclic adenosine monophosphate Ca^{2+} [33]. A consequence of the defect in chloride secretion of the crypt cells, is probably dehydration of the mucus layer, producing decreased transport and creating a risk of luminal obstruction, as in the bronchial tree.

Malabsorption is very common in CF with only 10% of patients showing a normal fat absorption.

Pancreatic insufficiency is present at birth in over 80% of patients due to an impairment of chloride and bicarbonate secretion [47]. Gasser et al. [30] recently found Cl^- secretion in the zymogen granules in pancreas and salivary glands in the rat and one may speculate on the importance of chloride secretion for the enzyme release in the human pancreas. The output of the digestive enzymes, particularly lipase, colipase and trypsin is diminished. Lingual lipase partly compensates for the deficiency of pancreatic lipase. This enzyme is acid resistent, and only inactivated at pH < 2.0–2.2, which makes it very effective in the stomach and, in CF-patients, also in the duodenum.

Carbohydrate digestion is not disturbed because of the amylase from other origins, particularly from swallowed saliva.

Although pancreatic enzyme deficiency is accepted as the most important factor in malabsorption, other factors have to be considered.

Fat absorption is considerably facilitated by micelle formation and its migration to the surface of the enterocyte [52]. In CF the mucus layer is increased, and forms a barrier for macro-molecules and aggregates such as micelles [99].

Bile salts play an important role in micelle formation. CF patients suffer from bile salt deficiency as result of an increased loss of bile salt in the stools. The cause of the increased faecal bile salt concentration is not clear. The uptake of individual bile salts studied in isolated membrane vesicles from the terminal ileum is normal in contrast to measurements on whole cells [25, 81]. In vivo uptake of single conjugated bile salts in the distal ileum is normal in CF [114]. Taurine deficiency in CF increases the glycine conjugated fraction of bile salts. The lower solubility of glycine conjugates may hamper the overall bile salt absorption and secondarily the fat absorption.

Intestinal transport, as estimated by the oral to caecum transit time, is 2–3 times longer than normal in CF [5]. This is probably related to the abnormal behaviour of the mucus. The consequences are variable, i.e. prolonged contact time has potentially beneficial effects on absorption, but also facilitates bacterial overgrowth.

Malnutrition and deficiencies are the consequence of malabsorption, infections, a diminished appetite, or more usually, the combination of these. Resting energy expenditure is significantly increased and correlates negatively with pulmonary function and nutritional status [118]. If severe enough, malnutrition may compromise immune responses and constitute a risk for infections, thus establishing a vicious circle.

Many CF-patients are deficient in essential fatty acids (EFA) and fat soluble vitamins, in particular vitamin E. Plasma of patients shows a decrease of the linoleic acid level and an increase of the palmoleic acid and oleic acid level.The EFA deficiency may be the consequence of fat malabsorption but could be directly related to the basic defect, a suggestion that is supported by the observation that EFA deficiency is also found in the absence of steatorrhoea [105]. Vitamin E deficiency is most pronounced under conditions of both pancreatic insufficiency and bile salt deficiency. Symptoms caused by vitamin E deficiency are rare and manifest only after long-standing extremely low serum levels. Deficiency of vitamin A is common in CF and symptoms of night blindness have been described. Vitamin D deficiency is rare, in particular in sunny climates. Vitamin K deficiency occurs in association with liver disease, inadequate intake and with the use of antibiotics.

Liver and bile duct pathology

Although approximately 30% of the CF patients older than 10 years of age have hepatomegaly, only a few have abnormal liver function tests (10%) or oesophageal varices (1%) [74]. The histopathology of the liver is characterised by focal biliary fibrosis which is probably due to progressive obstruction of the bile ducts [96]. Chloride-bicarbonate exchange and chloride conductance have been demonstrated in the canalicular membrane of bile ducts [61, 79], and these may play a role in bile formation. Malnutrition, bile salt deficiency and EFA deficiency are probably also involved in the pathogenesis of liver cirrhosis in CF. Large amounts of conjugated bile salts are lost in the stools resulting in depletion of the taurine pool [113] and domination of glycine conjugates which are less soluble.

Recent studies describe abnormalities of the extrahepatic bile ducts, which can contribute to the development of cirrhosis [29, 66, 106]. Gaskin et al. [29] found symptoms of liver disease in 40% of 153 CF patients. The majority of these patients showed abnormalities in the biliary tract when studied by scintigraphy and cholangio-

graphy. The disorders ranged from strictures in the common bile duct to narrowing and beading of the intrahepatic ducts.

A severe complication is portal hypertension and upper gastro-intestinal haemorrhage. Death may occasionally be due to liver failure.

Therapy for malabsorption and malnutrition

Malabsorption in CF can be improved by giving pancreatic extracts with meals [6, 97]. An important advance has been enteric coated microspheres resistant to acid which significantly enhances the enzyme activity in the duodenum. Instead of large amounts of pancreatic powder, only two or three capsules a meal are required for correction of malabsorption. However, intestinal absorption can only partly be corrected in most of the patients. Possible explanations for this are bile salt deficiency and the mucus barrier, which also limits absorption. Several investigators suggested that taurine supplementation improved fat absorption [15], but these results were not confirmed by others [115]. At present the usefulness of taurine supplementation is a subject of further investigation.

A high energy intake is necessary for many patients, but this is often difficult to achieve [118]. Several methods have been introduced to increase energy supply [8, 95]. The efficacy of additional calories on nutritional status and pulmonary function has been investigated by many studies [118]. Most investigations on nutritional rehabilitation are short-term studies and show only transient improvement in nutritional status. In most studies the pulmonary function either did not change or showed a gradual decline. Long term hyperalimentation however may prevent further deterioration of lung function [8,95]. A comparison between different dietary strategies in two populations revealed that a normal fat intake was associated with a higher survival age and a taller stature compared to a restricted fat intake, but had no influence on lung function [16]. It is our experience that lung infections are often accompanied by a decrease in body weight [67]. To what extent maintenance of optimal nutritional condition will prevent pulmonary deterioration has not yet been answered. Important points are: a strict adherence to the diet; involvement by a team of food-technicians, dieticians and nurses; and most importantly palatable food.

An increase in recommended daily allowance with 30%–50% for compensation of the extra losses and the increased energy expenditure is recommended. Fat should provide 40% of the daily energy in the diet and EFA 2%–5%. Medium chain triglyceride fat is not recommended because of poor taste and high costs. Polyunsaturated fatty acids are preferred because of their increased digestibility. If extra calories are needed, glucose polymers may be used. Vitamin supplements are necessary and should preferably given in water soluble form (Table 2). Trace elements, particular zinc, are only prescribed in young infants with growth failure and during parenteral nutrition.

Table 2. Daily vitamin supplements in CF (serum levels in μmol/1)

	Normal	Moderate deficient	Severe deficient
Vitamin A serum level	1.2–3.9	0.5–1.2	< 0.5
Dosage	1300–2400	9000 IU	18000 IU
Vitamin D serum level	30–100	10–30	< 10
Dosage	400–800	3000 IU	6000 IU
Vitamin E serum level	18–37	10–18	< 10
Dosage	50 mg	125 mg	250 mg

The vitamin preparations must be prescribed in the water soluble form. In case of deficient serum level and high dosage, the levels must be controlled regularly.

The administration of enteric nutrients in practice is complicated.

Nasogastric tube feeding at night is an effective procedure, but continuous pancreatic enzyme supplementation is a problem and therefore an elemental diet is advocated. Not all patients tolerate a nasogastric tube, and in addition, it may promote gastro-oesophageal reflux [91] with a potential risk for aspiration.

Gastrostomy feeding has similar drawbacks. Jejunostomy is often well tolerated but continuous infusion is necessary to prevent dumping. Recurrent surgical procedures and anaesthesia may be required in many patients and an abdominal fistula is a psychological burden for most patients.

Parenteral nutrition is difficult to perform and needs a skilled team. To make a decision for an individual patient one has to balance the need to supply extra calories and the feasibility of the various procedures for that particular patient [4, 53]. In practice these procedures have to be considered in patients with a markedly depressed appetite and severe malnutrition, although there is an ongoing discussion on the potential benefit of intervention at an earlier stage.

Complications

Intestinal motility and abstruction. It is important to consider the possibility of gastro-oesophageal reflux in CF patients with upper abdominal symptoms or complaints of progressive respiratory symptoms. Regurgitation and heartburn were significantly more frequent in CF patients as compared with normals [91]. Pathological reflux studied with 24 h oesophageal pH monitoring was found in approximately 25% of the patients, but signs of aspiration were not detected.

Meconium ileus (MI) is the presenting symptom in 10% of CF patients. The mortality was high until the establishment of reliable surgical techniques 20 years ago; thereafter a pronounced increase in survival (from 55% to 96%) in the 1st year of life was observed [45]. MI is more frequent in families with other siblings suffering from CF. Although it is speculated that children with MI have a different haplotype, these patients show a similar course of the disease as patients without MI [65].

Intestinal obstruction may occur later in life, when it is described as either the "meconium ileus equivalent syndrome" or, better "distal intestinal obstruction syndrome" (DIOS). This condition is due to mucus impaction, comparable to the situation in MI. Abdominal pain is the most common manifestation. DIOS is estimated to occur in approximately 20% of the older CF patients, and is limited to patients with pancreatic insufficiency, suggesting a direct relationship with malabsorption of nutrients. An indirect relationship is supported by the fact that intestinal obstruction does not occur in non-CF types of exocrine pancreatic insufficiency [37].

The conventional therapy for DIOS consists of oral N-acetyl-cystein, but the results are often disappointing. Lactulose is sometimes helpful. DIOS can be treated by gastrografin enema of the colon, but this treatment is painful and has the risk of dehydration and intestinal perforation. Oral gastrografin dosages were effective in a dosage of 50 ml in children under 8 years of age and 100 ml in older children and adults, diluted in a 4 fold volume of water [68]. In two studies [13, 18] the use of a rapid gastrointestinal lavage with a balanced electrolyte solution was found to be effective. Most of the children were able to drink up to 1000 ml/h with a total volume of 4–6 l but nausea was a frequent side-effect.

Portal hypertension

Until the 1970s portal hypertension and oesophageal varices were treated by porto-caval shunts and splenorenal shunts. Although most of these patients were at risk because of diminished lung function, the results were satisfactory [120]. Sclero-therapy is usually found to prevent recurrent bleeding [101] and is presently considered a first choice.

Liver insufficiency in CF patients must be treated as in non-CF patients with protein restricted diet, diuretics and lactulose. Some patients with terminal liver insufficiency recieved transplantation [63]. This approach raises many technical and ethical questions, which are presently under discussion.

Perspectives

Rapidly developing knowledge of the pathophysiology of CF will probably result in new possibilities in diagnosis and treatment in the not too distant future. Sensitive indices to assess disease activity will facilitate optimal therapy. Therapy at home will reduce the necessity for frequent hospitalisation thereby improving the quality of life [11,19]. Prenatal diagnosis by DNA technology and screening will ultimately result in a lower incidence of CF. Correction of the basic defect (gene therapy) may also be considered a possibility.

References

1. Abman SH, Ogle JW, Butler SN, Rumack CM, Accurso FJ (1988) Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. J Pediatr 113:826–830
2. Ammitzoll T, Pederson SS, Espersen F, Schiller H (1988) Excretion of urinary collagen metabolites correlates to severity of pulmonary disease in cystic fibrosis. Acta Paediatr Scand 77:842–846
3. Andersen DH (1939) Cystic fibrosis of the pancreas and its relation to celciac disease: a clinical and pathological study. Am J Dis Child 56:344
4. Anonymous (1986) Supplementary nutrition in cystic fibrosis. Lancet I:249–251
5. Bali B, Stableforth DE, Asquith P (1983) Prolonged small-intestinal transit time in cystic fibrosis. Br Med J 287:1011–1013
6. Beverly DW, Kelleher J, MacDonald A, Littlewood JM, Robinson T, Walters MP (1987) Comparison of four pancreatic extracts in cystic fibrosis. Arch Dis Child 62:564–568
7. Bijman J, Fromter E (1987) Direct demonstration of high transepithelial chloride conductance in normal human sweat-duct which is absent in cystic fibrosis. Pflugers Arch 407 [Suppl 2]:S123–S127
8. Boland MP, Stoski DS, MacDonald NE, Soucy P, Patric J (1986) Chronic jejunostomy feeding with a non-elemental formula in undernourished patients with cystic fibrosis. Lancet I:232–234
9. Bossa JA, Black PG (1988) Controlled trial of astreonam vs tobramycin and azlocillin for acute pulmonary exacerbations of cystic fibrosis. Pediatr Infect Dis J 7:171–176
10. British Thoracic Society Research Committe (1985) Ceftazidime compared with gentamycin and carbenicillin in patients with cystic fibrosis, pulmonary Pseudomonas infection and an exacerbation of respiratory symptoms. Thorax 40:358–363
11. Brown-Enring LT, Finkelstein SM, Budd JR, Kujawa SJ, Wielinski CL, Warwick WJ, Nguyen S (1988) Implimentation of a home-based program for early detection of clinical deterioration in cystic fibrosis. Med Instrum 22:240–246
12. Carswell F, Ward C, Cook DA, Speller DG (1987) A controlled trial of nebulised aminoglycoside and oral flucloxacillin versus placebo in the outpatient management of children with cystic fibrosis. Br J Dis Chest 81:356–360
13. Cleghorn GJ, Stringer DA, Forstner GG, Durie PR (1986) Treatment of distal intestinal obstruction syndrome in cystic fibrosis with a balanced intestinal lavage solution. Lancet I: 8–11
14. Cohn RC, Jacobs M, Aronoff SC (1988) In vitro activity of amiloride combined with tobramycine against Pseudomonas isolates from patients with cystic fibrosis. Antimicrob Agents Chemother 32:395–396
15. Colombo C, Arlati S, Curcio R, Maiavacca R, Garatti M, Ronchi M, Corbetta C, Giunta A (1988) Effect of taurine supplementation on fat and bile acid absorption in patients with cystic fibrosis. Scand J Gastroenterol 23 [Suppl 143]: 151–156
16. Corey M, McLaughlin FJ, Williams M, Levison H (1988) A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. J Clin Epidemiol 41:583–591
17. Cystic Fibrosis Foundation (1983) Pulmonary infection in cystic fibrosis. GAP Conference Report 7:4
18. Davidson AC, Harrison K, Steinfort CL, Geddes DM (1987) Distal intestinal obstruction syndrome in cystic fibrosis treated by oral intestinal lavage, and a case of recurrent obstruction despite normal pancreatic function. Thorax 42:538–541
19. Donati MA, Guenette G, Auerbach H (1987) Prospective controlled study of home and hospital therapy of cystic fibrosis pulmonary disease. J Pediatr 111:28–33
20. Fanconi G, Uehlinger E, Knauer C (1936) Das Colliakiesyndrom bei angeborener Zysticker Pancreas Fibromatose und Bronchiektasien. Wien Med Wochenschr 86:753
21. Fass RJ (1982) Comparative in vitro activities of azlocillincefotaxime and azlocillin-tobramycin combinations against blood

and multi-resistant bacterial isolates. Antimicrob Agents Chemother 22:167–169
22. Feanny S, Forsyth S, Corey M, Levison H, Zimmerman B (1988) Allergic broncho-pulmonary aspergillosis in cystic fibrosis: a secretory immune response to a colonizing organism. Ann Allergy 60:64–68
23. Fellows KE, Khaw K-T, Schuster S, Shachman H (1979) Bronchial artery embolization in cystic fibrosis. Technique and longterm results. J Pediatr 95:959–965
24. Fick RB, Baltimore RS, Squier SU, Reynolds HY (1985) The immunoglobulin C proteolytic activity of Pseudomonas aeruginosa in cystic fibrosis. J Infect Dis 151:589–598
25. Fondacaro JD, Heubi JE, Kellogg FW (1982) Intestinal bile acid malabsorption in cystic fibrosis: a primary mucosal cell defect. Pediatr Res 16:494–498
26. Forsyth KD, Hohnman AW, Martin AJ, Bradley J (1988) IgG antibodies to Aspergillus fumigatus in cystic fibrosis: a laboratory correlate of disease activity. Arch Dis Child 63: 953–957
27. Freye HB, Kurtz SM, Spock A, Capp MP (1964) Light and electron microscopic examination of the small bowel of children with cystic fibrosis. J Pediatr 64:575–579
28. Gardner ID (1981) Suppression of antibacterial immunity by infection with influenzae virus. J Infect Dis 144:225–231
29. Gaskin KJ, Waters DLM, Howman-Giles R, De Silva M, Earl JW, Martin HCO, Kan AE, Brown JM, Dorney SFA (1988) Liver disease and common-bile-duct stenosis in cystic fibrosis. N Engl J Med 318:340–346
30. Gasser KW, DiDomenico J, Hopfer U (1988) Potassium transport by pancreatic and parotid zymogen granule membranes. Am J Physiol 255:PC 705–711
31. Gold R (1987) Mild to moderate chest exacerbations: do antibiotics help? Pediatr Pulmonol [Suppl] 1:38–39
32. Gold R, Jin E, Levison H, Isles A, Fleming PC (1983) Ceftazidime alone and in combination in patients with cystic fibrosis: lack of efficacy in treatment of severe respiratory infections caused by Pseudomonas cepacia. J Antimicrob Chemother 12 [Suppl A]:331–336
33. Goldstein JL, Nash NT, AL-Bazzaz F, Layden TJ, Rao MC (1988) Rectum has abnormal ion transport but normal cAMP-binding proteins in cystic fibrosis. Am J Physiol 254:C719–C724
34. Goldstein W, Döring G (1986) Lysosomal enzymes and proteinase inhibitors in the sputum of patients with cystic fibrosis. Am Rev Respir Dis 154:49–56
35. Groot R de, Smith AL (1987) Antibiotic pharmacokinetics in cystic fibrosis. Differences and clinical significance. Clin Pharmacokin 13:228–253
36. Halley DJJ, Bijman J, Jonge HR de, Sinaasappel M, Neijens HJ, Niermeijer MF (1990) The cystic fibrosis defect approached from different angles. New perspectives on the gene, the chloride channel, diagnosis and therapy. Eur J Pediatr 149: 670–677
37. Hanly JG, Fitzgerald MX (1983) Meconium ileus equivalent in older patients with cystic fibrosis. Br Med J 286:1411–1412
38. Hodson ME, Winfield HJ, Batten JC (1983) Tobramycin and carbenicillin compared with gentamycin and carbenicillin in the treatment of infection with Pseudomonas aeruginosa in adult patients with cystic fibrosis. Br J Dis Chest 77:71–77
39. Høiby N (1982) Microbiology of lung infections in cystic fibrosis patients. Acta Paediatr Scand 30 [Suppl 301]:33–54
40. Høiby N, Friis B, Jensen K, Koch C, Møller NE, Støving S, Szaff M (1982) Antimicrobial chemotherapy in cystic fibrosis patients. Acta Paediatr Scand 301 [Suppl]:75–100
41. Hollsing AE, Lantz B, Bergstrom K, Snalmborg AS, Strandvik B (1987) Granulocyte elastase-alpha 1 antiproteinase complex in cystic fibrosis: sensitive plasma essay for monitoring pulmonary infections. J Pediatr 111:206–211
42. Horrevorts AM, Degener JE, Dzoljic-Danilovic G, Michel MF, Kerrebijn KF, Driessen O, Hermans J (1987) Pharmacokinetics of tobramycin in patients with cystic fibrosis. Chest 88: 260–264
43. Isles A, Maclutkey I, Corey M, Gold R, Prober C, Fleming PC, Levinson H (1984) Pseudomonas cepacia infection in cystic fibrosis: an emerging problem. J Pediatr 104:206–210
44. Kattwinkel J, Faussig LM, McIntosh CL, di Sant'Aqnese PA, Boat TM, Wood RE (1973) Intrapleural installation of quinacrine for recurrent pneumothorax use in a patient with cystic fibrosis. JAMA 226:557–561
45. Kerem E, Corey M, Kerem B, Durie P, Tsui LC, Levison H (1989) Clinical and genetic comparisons of patients with cystic fibrosis, with or without meconium ileus. J Pediatr 114:767–773
46. Klinger JD, Tandler B, Libdtke CM, Boat TF (1984) Proteinases of Pseudomonas aeruginosa evoke mucin release by tracheal epithelium. J Clin Invest 74:1669–1678
47. Kopelman H, Corey M, Gaskin K, Durie P, Weizman Z, Forstner G (1988) Impaired cloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas. Gastroenterology 95:349–355
48. Kriloff L, Owens G, Rogers R, Mascococco M (1985) Does chest physical therapy work? Chest 88:436–444
49. Krilov LR, Blumer IL, Stern RC, Hartsein AL, Igleroski BN, Goldman DA (1985) Imipenem/cilastatin in acute pulmonary exacerbations of cystic fibrosis. Rev Infect Dis 7:5482–5489
50. Lebel MH, McCracken GH jr (1988) Astreonam: view of the clinical experience and potential uses in pediatrics. Pediatr Infect Dis 7:331–339
51. Leclercq-Foucart J, Forget PP, Van Cutsem JL (1978) Lactulose-rhamnose intestinal permeability in children with cystic fibrosis. J Pediatr Gastroenterol Nutr 6:66–70
52. Levitt MD, Kneip JM, Levitt DG (1988) Use of laminar flow and unstirred layer models to predict instestinal absorption in the rat. J Clin Invest 81:1365–1369
53. Levy L, Durie P, Pencharz P, Corey M (1986) Prognostic factors associated with patient survival during nutritional rehabilitation in malnourished children and adolescents with cystic fibrosis. J Pediatr Gastroenterol Nutr 5:97–102
54. Liebman J, Lucas R, Moss A, Cotten E, Rosenthal A, Ruttenberg H (1976) Airline travel for children with chronic pulmonary disease. Report of the cardiovascular committee of the Cystic Fibrosis Foundation. Pediatrics 57:408–412
55. Mager C, Williams MH jr (1982) Treatment of massive hemoptysis with intravenous pitressin. Lung 160:165–169
56. Mann HJ, Canafar CJ, Cipolle RJ, Daniels CE, Zaske ED, Warwick WJ (1985) Increased dosages requirements of tobramycin and gentamycin for treating pseudomonas pneumonia in patients with cystic fibrosis. Pediatr Pulmonol 1:238–243
57. Maquire S, Moriarty P, Tempany E, Fitzgerald M (1988) Unusual clustering of allergic bronchopulmonary aspergillosis in children with cystic fibrosis. Pediatrics 82:835–839
58. Martin AJ, Smalley CA, George RH, Healing DE, Anderson CM (1980) Gentamicin and tobramycin compared to the treatment of mucoid Pseudomonas lung infections in cystic fibrosis. Arch Dis Child 55:604–607
59. Mastella G, Agostini M, Barlocco G, Buonomi U, Borgo G, Buzzino L, Cabrini G, Cappellette LM, Castelani L, Conforti M, Marazzani S, Martini N, Montemezzi P, Poulon G, Pederzini F, Sancasani L, Scroccaro G (1983) Alternative antibiotics for the treatment of Pseudomonas infections in cystic fibrosis. J Antimicrob Chemother 12 [Suppl A]:297–311
60. McLaughlin FJ, Matthews WJ, Strieder DJ, Sullivan B, Taneja A, Murphy H, Goldman DA (1983) Clinical and bacteriological responses to three antibiotic regimens for acute exacerbations of cystic fibrosis: ticarcillin-tobramycin, azlocillin-tobramicin and azlocillin-placebo. J Infect Dis 147:559–567
61. Meier PJ, Knickelbein R, Moseley RH, Dobbins JW, Boyer JL (1985) Evidence for carrier-mediated chloride/bicarbonate exchange in canalicular rat liver plasma membrane vesicles. J Clin Invest 75:1256–1263
62. Mendelman PM, Smith AC, Levy J, Weber A, Ramsey B, Davis RL (1985) Aminoglycoside penetration, inactivation and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 132: 761–765

63. Mieles LA, Orenstein D, Teperman L, Podesta L, Konesu B, Starzl TE (1989) Liver transplantation in cystic fibrosis. Lancet I:1073
64. Möller NE, Koch C, Vesterhange S, Jensen K (1982) Treatment of pulmonary Pseudomonas aeruginosa infection in cystic fibrosis with cefsulodin. Scand J Infect Dis 14:207–211
65. Mornet E, Serre JL, Farrall M, Boue J, Simon-Bouy B, Estivill X, Williamson R, Boue A (1988) Genetic differences between cystic fibrosis with and without meconium ileus. Lancet I:376–378
66. Nagel RA, Javaid A, Meire HB, Wise A, Westaby D, Kavani J, Lombard MG, Williams R, Hodson ME (1989) Liver disease and bileduct abnormalities in adults in cystic fibrosis. Lancet II:1422–1425
67. Neijens HJ, Duiverman EJ, Kerrebijn KF, Sinaasappel M (1988) Influence of respiratory exacerbations of lung function variables and nutritional status in CF patients. Acta Pediatr Scand [Suppl] 317:38–41
68. O'Halloran SM, Gilbert J, McKendrick OM, Carty HML, Heaf DP (1986) Gastrografin in acute meconium ileus equivalent. Arch Dis Child 61:1128–1130
69. Orenstein DM (1988) Exercise tolerance and exercise conditioning in children with chronic lung disease. J Pediatr 112: 1043–1047
70. Padoan R, Cambisano W, Costantini D, Crossignani RM, Danza ML, Trezzi G, Giunta A (1987) Ceftazidime monotherapy vs combined therapy in pseudomonas pulmonary infections in cystic fibrosis. Pediatr Infect Dis 6:648–653
71. Pedersen SS, Jensen T, Osterhammel D, Osterhammel P (1987) Cummulative and acute toxicity of repeated high-dose tobramycin treatment in cystic fibrosis. Antimicrob Agents Chemother 31:594–599
72. Pedersen SS, Pressler T, Jensen T, Rosdahl VT, Bentzon MW, Høiby N, Koch C (1987) Combined imipenem/cilastatin and tobramycin therapy of multiresistant Pseudomonas aeruginosa in cystic fibrosis. J Antimicrob Chemother 19:101–107
73. Penketh ARL, Hodson ME, Batten JC (1983) Ticarcillin compared with carbenicillin in the treatment of exacerbations of bronchopulmonary infection in cystic fibrosis. Br J Dis Chest 79:179–184
74. Penketh ARL, Wise A, Mearns MB, Hodson ME, Batten JC (1987) Cystic fibrosis in adolescents and adults. Thorax 42: 526–532
75. Petersen NF, Høiby N, Mordhorst CH, Lind K, Flensborg EW, Bruin B (1981) Respiratory infections in cystic fibrosis patients caused by virus, chlamydia and mycoplasma, possible synergism with Pseudomonas aeruginosa. Acta Paediatr Scand 70:623–628
76. Pier GB (1985) Pulmonary disease associated with Pseudomonas aeruginosa in cystic fibrosis: current status of the host-bacterium interaction. J Infect Dis 151:575–580
77. Pollack M, Anderson SE (1978) Toxicity of Pseudomonas aeruginosa exotoxin A for human macrophages. Infect Immun 19:1091–1096
78. Ramphal R, Lhermitte M, Filliat M, Roussel P (1988) The binding of anti-pseudomonal antibiotics to macromolecules from cystic fibrosis sputum. J Antimicrob Chemother 22:483–490
79. Reuben A (1984) Bile formation: sites and mechanisms. Hepatology 4:15S–24S
80. Roe EA, Jones RJ (1974) Intracellular killing of different strains of Pseudomonas aeruginosa by human leukocytes. Br J Exp Pathol 55:336–343
81. Rooy FWM de, Van den Berg JWO, Sinaasappel M, Bosman-Jacobs EP, Touw-Blommesteijn AC (1985) Bile acid malabsorption in cystic fibrosis; membrane vesicles, a tool for revealing the role of the ileal brush border membrane. Acta Paediatr Scand [Suppl] 317:28–30
82. Sant'Agnese PA di, Darling RC, Perera GA, Shea E (1953) Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas. Clinical significance and relationship to the disease. Pediatrics 12:549
83. Schaad UB, Kraemer R, Gaze H, Hadorn B (1978) One-hour blood-xylose in cystic fibrosis. Arch Dis Child 53:756–757
84. Schaad UB, Des Grand Champs D, Kraemer R (1986) Antimicrobial therapy of Pseudomonas pulmonary exacerbations in cystic fibrosis: a prospective evaluation of netilmycin plus azlomicin: metilmicin plus ticarcillin. Acta Paediatr Scand 75: 128–138
85. Schaad UB, Wedgewood-Krucks J, Suter S, Kraemer R (1987) Efficacy of inhaled amikacin as adjunct to intravenous combination therapy in cystic fibrosis. J Pediatr 111:599–605
86. Schlesinger E, Miller W, Hardt H van der, Sching E, Rieger CHL (1985) Effect of longterm continuous anti-staphylococcal antibiotic treatment in young children with cystic fibrosis. In: Lawson D (ed) Cystic fibrosis horizons. Wiley, New York, p 280
87. Schnheyder H, Jensen T, Høiby N, Koch C (1988) Clinical and serological survey of pulmonary aspergillosis in patients with cystic fibrosis. Int Arch Allergy Appl Immunol 85:472–477
88. Schwartzman S, Boring JR (1971) Antiphagocytic effect of slime from a mucoid strain of Pseudomonas aeruginosa. Infect Immun 3:762–767
89. Shwachmann H, Kulczycki LL (1958) Longterm study of 105 patients with cystic fibrosis: studies made over a 5 to 14 year period. Am J Dis Child 96:6–10
90. Scott J, Higenbottom T, Hutter J, Hodson M, Stewart S, Penketh A, Wallwork J (1988) Heart-lung transplantation for cystic fibrosis. Lancet II:192–241
91. Scott RB, O'Loughlin EV, Gall DG (1985) Gastrooesophageal reflux in patients with cystic fibrosis. J Pediatr 106:223–227
92. Scribner RK, Marks MI, Weber AH, Tarpey MM, Welch DF (1982) Activities of various beta-lactam and aminoglycosides, alone and in combination against isolates of Pseudomonas aeruginosa from patients with cystic fibrosis. Antimicrob Agents Chemother 21: 939–943
93. Scully BE, Nakatomi M, Ores C, Davidson S, Neu HC (1987) Ciprofloxacin therapy in cystic fibrosis. Am J Med 82:196–201
94. Seddon DJ, Hodson ME (1988) Surgical management of pneumothorax in cystic fibrosis. Thorax 43:739–740
95. Shepherd RW, Holt TL, Thomas BJ, Kay L, Isles A, Francis PJ, Ward LC (1986) Nutritional rehabilitation in cystic fibrosis: controlled studies of effects on nutritional growth retardation, body protein turnover, and course of pulmonary disease. J Pediatr 109:788–794
96. Sinaasappel M (1990) Hepatobiliary pathology in patients with cystic fibrosis. Acta Pediatr Scand [Suppl] 363:45–51
97. Sinaasappel M, Bouquet J, Neijens HJ (1985) Problems in the treatment of malabsorption in CF. Acta Pediatr Scand [Suppl] 317:22–27
98. Smith MJ, Hodson ME, Batten JC (1986) Ciprofloxacin in cystic fibrosis. Lancet I:1103
99. Smithson KW, Millar DB, Jacobs LR, Gary GM (1981) Intestinal diffusion barrier: Unstirred water layer or membrane surface mucous coat? Science 214:1241–1244
100. Spector ML, Stern RC (1989) Pneumothorax in cystic fibrosis, a 26-year experience. Ann Thorax Surg 47:204–207
101. Stamatakis JD, Howard ER, Psacharopoulos HT, Mowat AP (1982) Injection sclerotherapy for oesophageal varices in children. Br J Surg 69:74–75
102. Stern RC, Wood RE, Boat FF, Matthew LW, Tucker AS, Doershuk CF (1978) Treatment and prognosis of massive hemoptysis in cystic fibrosis. Am Rev Respir Dis 117:825–890
103. Stowe SM, Boat FF, Mendelsohn H, Stern RC, Tucker AS, Doershuk CF, Matthew LW (1975) Open thoracotomy for pneumothorax in cystic fibrosis. Am Rev Respir Dis 11:611–616
104. Strandvik B (1984) Adverse reactions to piperacillin in patients with cystic fibrosis. Lancet I:1362

105. Strandvik B, Brönnegard M, Gilljam H, Carlstedt-Duke J (1988) Relation between defective regulation of arachidonic acid release and symptoms in cystic fibrosis. Scand J Gastroenterol 23 [Suppl 143]: 1–4
106. Strandvik B, Hjelte L, Gabrielsson N, Glaumann H (1988) Sclerosering cholangitis in cystic fibrosis. Scand J Gastroenterol 23 [Suppl 143]: 121–124
107. Suter S, Schaad UB, Roux L, Nijdegger UE, Waldvogel FA (1984) Granulocyte neutral proteases and Pseudomonas elastase as possible causes of airways damage in patients with cystic fibrosis. J Infect Dis 149: 523–527
108. Suter S, Schaad UB, Morgenthaler JJ, Chevalier I, Schnebli HP (1988) Fibronectin-clearing activity in bronchial secretions of patients with cystic fibrosis. J Infect Dis 158: 89–100
109. Sutton PF, Lopez-Vidriers MT, Paria DNSP, Clay MM, Webber B, Parker RA, Clarke SW (1985) Assessment of percussion, ribratory-shaking and breathing exercise in chest physiotherapy. Eur J Respir Dis 66: 147–152
110. Szaff M, Høiby N (1982) Antibiotic treatment of Staphylococcus aureus infection in cystic fibrosis. Acta Paediatr Scand 71: 821–826
111. Thomassen MJ, Klinger JD, Badger SJ, Heeckeren DW van, Stern RC (1984) Cultures of thoracotomy specimens confirm usefulness of sputum cultures in cystic fibrosis. J Pediatr 104: 352–356
112. Thomassen MJ, Demko CA, Klinger JD, Stern RC (1985) Pseudomonas cepacia colonization among patients with cystic fibrosis. Am Rev Respir Dis 131: 791–796
113. Thompson GN (1988) Excessive fecal taurine loss predisposes to taurine deficiency in cystic fibrosis. J Pediatr Gastroenterol Nutr 7: 214–219
114. Thompson GN, Davidson GP (1988) In vivo bile acid uptake from terminal ileum in cystic fibrosis. Pediatr Res 23: 323–328
115. Thompson GN, Robb TA, Davidson GP (1987) Taurine supplementation, fat absorption, and growth in cystic fibrosis. J Pediatr 111: 501–506
116. Thompkins LS (1985) DNA methods of clinical microbiology. In: Lennette EH, Balows A, Hausler WJ, Shadomy HJ (eds) Manual of clinical microbiology. American Society for Microbiology, Washington DC, pp 1023–1028
117. Tyrell JC, Hiller EJ, Martin J (1986) Face mask physiotherapy in cystic fibrosis. Arch Dis Child 61: 598–611
118. Vaisman N, Pencharz PB, Corey M, Canny GJ, Hahn E (1987) Energy expenditure of patients with cystic fibrosis. J Pediatr 111: 496–500
119. Versteegh FGA, Bogaard JM, Raatgever IW, Stam H, Neijens HJ, Kerrebijn KF (1990) Relationship between airway obstruction desaturation during exercise and nocturnal hypoxemia in cystic fibrosis patients. Eur Respir J 3: 68–73
120. Vroonhoven TJ van, Molenaar JC (1979) Distal splenorenal shunt for decompression of portal hypertension in children with cystic fibrosis. Surg Gynecol Obstet 149: 559–561
121. Weber B, Mickol MM, Jagger KS, Sallinger CB (1982) Interaction of Pseudomonas exoproducts with phagocytic cells. Can J Microbiol 28: 679–685
122. Wheeler WR, Williams M, Matthews JN, Colten HR (1984) Progression of cystic fibrosis lung disease as a function of serum immunoglobulin G levels, a 5 year longitudinal study. J Pediatr 104: 695–699
123. Wismiesky JJ, Todd EW, Fuller RK, Jones PK, Dearborn DG, Boat TP, Naff GB (1985) Immune complexes and complement abnormalities in patients with cystic fibrosis. Am Rev Respir Dis 132: 776–781