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Consensus report

Early intervention and prevention of lung disease in cystic fibrosis: a European consensus☆

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Abstract

In patients with cystic fibrosis (CF), early intervention and prevention of lung disease is of paramount importance. Principles to achieve this aim include early diagnosis of CF, regular monitoring of the clinical status, various hygienic measures to prevent infection and cross-infection, early use of antibiotic courses in patients with recurrent or continuous bacterial colonisation and appropriate use of chest physiotherapy.

Keywords: Lung disease; Cystic fibrosis; European consensus

1. Introduction

Cystic fibrosis (CF) is the most common autosomal recessive lethal hereditary disorder in Caucasians [1]. The prognosis of the disease is substantially dependent on chronic respiratory infection and inflammation, a hallmark of CF. *Pseudomonas aeruginosa* is the dominant pathogen today in patients with CF [2]. During the last decades, a variety of treatment strategies have been developed, including improved antibiotic therapies, which have had a significant positive impact on prognosis. The median survival age of individuals with CF in industrialized countries increased from 14 years in 1969 to more than 30 years in 2001 and approximately 37% of patients are 18 years of age or older

☆ In memoriam of Christian Koch. This document is the result of an European Consensus Conference which took place in Artimino, Tuscany, Italy, in March, 28–30, 2003, involving 37 experts on antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis patients, organized by the European Cystic Fibrosis Society, and sponsored by Chiron, Forest Belpharma and Hoffmann-La Roche. The purpose of the conference was to develop a consensus document on Early Intervention and Prevention of Lung Disease In Cystic Fibrosis based on current evidence.

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[2]. European registries report similar median survival ages [3,4].

However, during the last 5 years, reported survival rates appear to have reached a plateau in some industrialized countries (e.g., Ref. [2]). The objective of this consensus document is to overcome this possible development by outlining further strategies to substantially increase life expectancy in CF. These include (1) neonatal screening of the general population to identify CF, (2) early initiation of antimicrobial and anti-inflammatory therapy in identified patients, (3) implementation of effective hygienic measures inside and outside of CF centres, and, (4) establishment of patient registries.

Neonatal screening programmes for CF have been implemented in several countries with a high incidence of CF, such as New Zealand, Australia, Austria, France, Northern Ireland, Scotland, Wales, some regions of England and some states in the USA. Early identification of patients with CF by neonatal screening reduces the time to diagnosis to a few weeks after birth. Clearly, any therapeutic approach can be initiated much earlier in identified patients, particularly antimicrobial therapy, since bacterial lung infections may start very early in the life of an infant with CF. Optimizing antibiotic therapy against the major CF pathogens and anti-inflammatory therapy is of the highest priority, since lung disease has a major impact on the prognosis of patients. Some years ago, the ECFS and UK CF Trust issued recommendations for the antibiotic treatment of *P. aeruginosa* [5,6]. However, much work has been done since then, and the present document will summarize the latest developments including strategies against pathogens other than *P. aeruginosa*. In addition, improved anti-inflammatory therapy, mucolytic therapy and airway physiotherapy as adjuncts to antibiotic therapy become more and more important and results will be presented here. Our growing knowledge regarding the transmission of bacterial pathogens from infected patients, contaminated healthy individuals, or the inanimate environment to patients with CF has resulted in the implementation of better infection control policies within CF centres to minimize transmission of infection between patients. Finally, due to the heterogeneity and changing epidemiology of the disease, we recommend the collection of patient data in registries to obtain sufficient statistical power to anticipate new developments and trends and to optimize care. This document provides a summary of the relevant data and evidence-based recommendations for the early intervention and prevention of lung disease in patients with CF to improve care in CF centres.

2. Screening

Population screening for CF can be carried out with the aim to identify CF carriers or patients. The goal of heterozygote screening is to provide carrier couples with the information that allows them to make an informed choice in family planning [7]. The ultimate goal of CF carrier screening is to reduce the number of CF births on a population level. However, there is little evidence that couples carrying the CF gene will actually avoid giving birth to an affected child. Nevertheless, since antenatal screening was offered for CF in Scotland, the number of births has fallen dramatically, indicting that in this area affected couples choose therapeutic abortion. Heterozygote screening can be offered preconceptionally or to the pregnant woman. According to recent guidelines, it is recommended that prenatal screening for CF is offered to every pregnant woman in the USA, but there is concern that the benefits and risks of these guidelines have not been investigated [8]. The objective of neonatal screening is to detect infants with CF as early in life as possible [9]. In infants with CF identified by neonatal screening, standard care may be initiated more rapidly than in CF infants diagnosed by symptoms and this may offer clinical benefit. Neonatal screening will allow early genetic counselling, specifically before the conception of another potentially affected child, and eventually may lead to changes in the reproductive behaviour of couples and their child bearing relatives with a first affected child [10,11]. Furthermore, it may be of benefit to parents by removing the stress of a delayed diagnosis [12].

Neonatal screening for CF has been implemented in several parts of the world [13]. Immunoreactive trypsinogen (IRT) followed by mutation analysis in samples with increased concentrations of IRT has proven to be a procedure with a high sensitivity as well as specificity in the diagnosis of CF [14]. Multiple CFTR alleles should be included to increase the sensitivity and the specificity of newborn screening programs employing two-tier testing with trypsinogen and DNA analysis [15,16]. Population-based studies have demonstrated [17] that CF diagnosed in the first weeks of life, before the appearance of symptoms results in better clinical condition later. For instance, in the Veneto region of Italy the rate of screening increased progressively from 1970 and currently ranges from 98.4% to 99.1% with a median time from birth to confirmation of diagnosis of 32 days (range: 0–1531) (B. Assael, personal communication).

The effects of neonatal screening on clinical outcome are more cumbersome to assess [7]. A blinded, prospective and randomized study [18,19] demonstrated that early recognition of the disease has nutritional benefits in the first years of life, at the time when growth is most rapid. After delayed diagnosis of CF, malnutrition may persist and catch-up may not be possible [19]. Poor nutritional status will be the results of delayed onset of enzyme substitution as well as delayed diagnosis and treatment of the lung infections. Several prospective cohort and controlled, but not randomized, studies have shown that neonatal diagnosis decreases the rate of hospitalisation [20,21] and leads to better clinical scores in childhood [12,22–25].

However, US registry-based data suggests that early asymptomatic diagnosis (<6 weeks of age) did not influence the rate of chronic infection by *P. aeruginosa*, a major factor in lung disease progression [26], probably reflecting the innate increased susceptibility of the CF airway for colonisation with opportunistic environmental pathogens and variable early treatment policies. Recent data in the UK CF Database also suggests that up to the age of 2 years, no benefit was observed for patients identified by screening in terms of the likelihood of acquisition of *P. aeruginosa* (Mehta et al., unpublished). However, in contrast to the American study [26], after the age of 2, significantly fewer patients diagnosed by screening had one or more *P. aeruginosa* positive cultures than those clinically diagnosed. This might be related to the opportunity screening offers to start treatment after the first acquisition of this pathogen. Improved survival for screened as compared to clinically diagnosed patients has been reported. For patients born between 1973 and 1980, survival rates of 88% and 80% in a screened group versus 60% and 50% in a clinically diagnosed group at age 11 and 24 years, respectively (excluding patients diagnosed by presence of meconium ileus), have been observed [23,27]. However, survival can no longer be used as a marker in this context because of the extended life expectancy following the more effective use of antibiotics, and improved nutritional management including supplementation with more effective acid resistant pancreatic enzymes, which has changed CF management since the mid-1980s. However, mortality in early infancy or childhood may be prevented using screening [28,29].

Furthermore, the median age of diagnosis of CF because of symptoms has been as low as 0.5–1 year of life in many regions, which differs substantially from neonatal screening allowing a diagnosis of CF around a median age of 4 weeks. Median life expectancy of patients with CF presently lies around the age of 30 years. Therefore, it is improbable that a diagnosis by neonatal screening has a large influence on survival. Besides CF is a heterogenous disease, and many factors may have influenced outcome over such a long period. Indeed, in a cohort study no significant difference in the overall cumulative probability of survival between patients diagnosed by neonatal screening or after symptoms has been observed in one area, although the survival curve of the patients detected by screening seemed to be the best [30]. It should be noted also that patients now aged 25 years and older did get their initial treatment in the mid 1970s, before acid resistant pancreatic enzyme replacement therapy was available.

Therefore, surrogate clinical measurements such as height, weight, lung function or microbiological status, rather than survival outcomes are better indicators of the benefit afforded by screening particularly during the first 10 years after birth when screening would be expected to have the greatest effect [17,18,27,31]. However, clinical benefit from neonatal screening is dependent on adequate treatment and the failure to provide an adequate standard of care after a diagnosis of CF has been made probably is a critical factor in outcome [32]. For example, a recent neonatal screening programme in CF [21] was not supported by initiation of a community based plan of optimised intervention at the time of diagnosis resulting in no clinical advantage.

In conclusion, it seems sufficiently clear that neonatal screening improves nutrition and growth, and probably leads to an improved lung function in the first 10 years of life. Other advantages are the low costs of screening. Early genetic counseling gives parents the choice of avoiding the birth of another child with CF [10] and leads to a reduction of the number of births of patients with CF on a population level [11]. Moreover, a short diagnostic delay appeared to be beneficial for parents with a child with CF [12]. The advantages of neonatal screening for CF while the procedure carries no harm of its own have led to the recommendation to consider screening for CF in every country with a routine neonatal screening programme and a high incidence of CF [11,20,33].

3. Early diagnosis of airway disease

The objective of early diagnosis of bacterial lung colonization/infection is to implement antibiotic therapy more rapidly, or even introduce it prophylactically, with the aim of influencing the outcome for the patient with CF. The spectrum of microbial pathogens in CF lung infections differs considerably from that of other patients with chronic lung disease. Many environmental bacteria are found in CF airway infections, including *S. aureus, P. aeruginosa, Stenotrophomonas maltophilia, B. cepacia* complex, fungi, atypical mycobacteria, whereas *Streptococcus pneumoniae, H. influenzae* or *Moraxella catarrhalis* and bacteria of the endogenous flora, which are often present in other lung diseases, are found less frequently. Furthermore, due to the chronic course of lung disease, bacterial pathogens such as *S. aureus* or *P. aeruginosa* change their phenotype and mucoid or small colony variants [34] are often observed which are not easily recognized by laboratories not specialized in CF microbiology. In addition, the stress of the local lung environment leads to the occurrence of hypermutable bacterial strains, which show a large variety of genotypic and phenotypic traits including resistance to antimicrobial drugs. Thus, sensitive and highly resistant colonies of a given strain may be present simultaneously in one sputum specimen. Since infection in patients with CF is often polybacterial, selective agars have to be used, particularly for *S. aureus, H. influenzae, P. aeruginosa, B. cepacia* complex and *atypical mycobacteria* ([5,35]; Table 1). Finally, the early diagnosis of lung infections in patients with CF is difficult, since lung infections are often already present in small children and infants not expectorating sputum [36–39]. Consequently, other methods such as nasopharyngeal aspirate, cough swabs, sputum induction

Table 1
Selective agars for identification of *S. aureus, H. influenzae, P. aeruginosa, B. cepacia* complex and *atypical mycobacteria*

Organism	Recommended media or processing[a]
S. aureus	Mannitol salt agar Columbia/colistin-nalidixic agar
H. influenzae	Chocolate agar (supplemented or not with 300 mg/l bacitracin) incubated anaerobically
P. aeruginosa	MacConkey agar, Difco Pseudomonas Isolation Agar
B. cepacia complex	BCSA, Mast cepacia agar
S. maltophilia	MacConkey agar, synergistic inhibition of beta-lactamase by aztreonam and clavulanic acid β-lactamase facilitates indification
A. xylosoxidan	MacConkey agar
Mycobacterial species other than tuberculosis (MOTT)	Decontamination step with 0.25% *N*-acetyl-L-cysteine and 1% NaOH followed by 5% oxalic acid, culture on Löwenstein-Jensen medium
Aspergillus spp.	*Aspergillus* spp. and other molds grow well on horse blood agar or Sabouraud agar selective for fungi
Other Gram-positives	Horse- or sheep blood agar, may be supplemented with neomycin and gentamicin (streptococcal selective agar)
Other Gram-negatives	MacConkey agar

For routine culture: Horse-blood agar, chocolate agar, MacConkey agar, mannitol salt agar, PC agar and Sabouraud agar. If acid fast bacilli are seen by microscopy: decontamination and Löwenstein-Jensen agar.

[a] Detection of some pathogens may be enhanced by prolonging incubation for as long as 4 days to allow slow-growing colonies to become apparent. All media are commercially available.

[41], bronchoalveolar lavage (BAL) [40] and even serological tests [42–44] have a role in diagnosis.

4. Patient registry

In patient registries (databases), clinical and epidemiological data from patients in a centre, a country or a region (such as Europe) are regularly collected to compare care and life expectancy of patients with CF between centres and countries and to observe trends in the changing epidemiology of the disease over time. Several CF registries have been developed [2,3,45–52]. Patient data collected in registries are meant to observe longitudinal changes in a given clinical/demographic parameter and to determine similarities/differences between centres/countries/regions at a given time for such parameters. This leads to analysis of the determinants for such similarities/differences resulting in changes and improvements of care.

Registry data help to establish descriptive statistics and demographic figures important as a basis for improvement of CF management and care. National and international registries should be linked in order to come to common methods of evaluation and to create more effective international guidelines. In addition to descriptive statistics, patient registries are a good basis for quality management including reports focussing on the quality of care in different institutions or cooperative groups. Quality ranking and benchmarking are identifying centres of excellence. Learning from best practice is a tool of quality management as well as a way of defining alarm signs and creating decision trees in defined situations of complication or deterioration. Quality groups can help to establish consensus statements and guidelines based on best practice.

Patient registries and quality management cannot replace scientific studies. For instance, representativity (annual return of data sheets) has been as low as 80% in Germany [3,49]. However, important questions can be asked and trends can be indicated that have to be checked by scientific studies. Most importantly, outcome data on different levels (survival, lung function, nutrition, microbiology) have to be compared with regard to different therapeutic strategies (e.g., centre care, antibiotic treatment, nutritional support). By longitudinal comparison predictive indicators in CF can be defined [53].

Registries are particularly important for CF, since the clinical disease spectrum is largely heterogenic and the outcome or clinical course is probably influenced by a variety of modifier genes [1]. Additionally, environmental factors may affect disease severity. Thus, certain CF subpopulations may only be detectable in large patient registries. Additionally, changes in the prevalence of CF pathogens important for the life expectancy of patients with CF are observed much earlier in the larger patient cohorts found in registries than in small patient cohorts. For example, while *S. aureus* and *H. influenzae* were the most prevalent pathogens in the pre-antibiotic era [54] and represented the major causes of morbidity and mortality in infants with CF at that time, *P. aeruginosa* is the dominating pathogen today [2]. However, this picture may change again. *S. maltophilia, Achromobacter (Alcaligenes) xylosoxidans, Aspergillus fumigatus*, non-tuberculous mycobacteria (NTM) and respiratory viruses are regarded as more and more important in the pathogenesis of lung disease in patients with CF.

Clearly, registries are expensive, and sponsorship for data collection and analysis is needed. In addition, a patient registry should be easily and rapidly accessible (possibly by Internet), and should contain anonymous and standardized data, which can be compared with other registries.

5. Strategies to eradicate bacterial pathogens from CF airways

The rationale for the question is that antimicrobial treatment may be necessary only when a microorganism is regarded as pathogenic in the CF airways. However, probably every microorganism whether regarded as a pathogen or not should be treated, since it causes inflammation which could damage airways. To determine if a microorganism is truly pathogenic in patients with CF an association of the organism with acute pulmonary exacerbations, increasing

chest radiographic signs of infection or altered high resolution chest CT images, development of an antibody response [55], a chronic decline in pulmonary function, and/or increased mortality has to be established [56]. The epidemiology of microbial pathogens in CF airways has changed over decades. Factors which may contribute to this change involve (1) antibiotic treatment, (2) increasing age of patients, (3) increased use of inhalation therapy combined with insufficient hygiene, and (4) evolution of the bacterial pathogens themselves.

5.1. Microbial pathogens

S. aureus is often the first microorganism isolated from CF sputum or cough swab in infants not receiving long-term anti-staphylococcal prophylaxis [2]. It was already recognized as a CF pathogen in the pre-antibiotic era [57] when it was responsible for the premature death of the majority of CF children [54]. The occurrence of methicillin resistant *S. aureus* (MRSA) strains among patients with CF in the last decade is particularly threatening [58], although at present does not seem to have clinical significance [59]. *P. aeruginosa*, particularly the mucoid colonial morphotype, was recognized as a pathogen in the 1970s [60]. In the majority of patients with CF producing sputum and carrying mucoid *P. aeruginosa*, the infection causes an immediate and more rapid reduction of lung function than in patients with CF without *P. aeruginosa* infection [55,61]. Higher sputum volumes are correlated with a greater degree of inflammation, higher neutrophil numbers and released serine proteinases and hence a greater degree of lung obstruction and destruction. Conversely, antibiotic treatment for *P. aeruginosa* in patients with CF had a positive effect on clinical condition, pulmonary function, *P. aeruginosa* colony counts in sputum, inflammatory markers, quality of life, nutritional status and survival of the patients [62–64].

Nonencapsulated *H. influenzae* has been recognized as a pathogen in CF for many decades [65] due to improved identification methods and selective conditions. It frequently persists in the lungs of patients with CF for prolonged periods of time and specific antibodies are found in the sputum and sera of these patients. Clear evidence of a pathogenic role for *H. influenzae* in individuals with CF is provided by measurement of inflammatory markers. In one study, some of the highest concentrations of C-reactive protein measured (>400 mg/l serum) were associated with acute exacerbations and culture of *H. influenzae* at $>10^8$ CFU/ml sputum [66]. Penetration of *H. influenzae* in epithelial cells may contribute to the persistence of this microorganism in patients with CF [67,68].

The *B. cepacia* (previously named *Pseudomonas cepacia*) complex is a group of at least nine closely related bacterial species [69,70], which emerged as CF pathogens in the last two decades. Many reports have confirmed that *B. cepacia* genomovar III (now known as *B. cenocepacia*) is highly transmissible and virulent in patients with CF [71]; infection with *B. cepacia* complex is associated with a markedly shortened median survival [47,53,72]. The ''*B. cepacia* syndrome'' is characterized by high fever, bacteremia, rapid pulmonary deterioration and death. Although infection with *B. cepacia* complex is generally chronic, in some patients with CF, infections may be transient.

S. maltophilia (previously named *Pseudomonas maltophilia* and subsequently *Xanthomonas maltophilia*) has been detected in sputum specimens of patients with CF. However, whether its detection is correlated with increased morbidity or mortality is unclear based on published evidence [73–77]. *S. maltophilia* prevalence rates vary considerably between CF centres with a mean prevalence rate of 4.3–6.4% [2,4] but up to 10% to 25% in single centres [76–78].

As with *S. maltophilia*, the opportunistic human pathogen *A.* (previously *Alcaligenes) xylosoxidans* has also been recovered with increasing frequency from respiratory tract cultures of patients with CF over the last decade [2]. Its pathogenicity in patients with CF is also rather unclear although an association of *A. xylosoxidans* with pulmonary exacerbation has been reported [79]. The prevalence rate of *A. xylosoxidans* recorded in clinical trials on inhaled tobramycin was 8.7%.

The prevalence of NTM has been determined as 13% (range: 7–24%) [80]. *Mycobacterium avium* complex (72%) and *M. abscessus* (16%) were the most common species [80]. The observation that patients with CF with repeated sputum isolates of non-tuberculous mycobacteria may develop typical clinical signs of mycobacteria disease [80–82], and show clinical improvements after courses of antimycobacterial therapy, supports the notion that NTM may be pathogens in CF [80,83–85]. Older age was the most significant predictor for isolation of NTM [80].

The virulence of *A. fumigatus* has been clearly established in patients with CF from 1970. Patients with CF produce specific antibodies against the microorganism [86], and *A. fumigatus*, as well as more rarely other fungi, may cause allergic bronchopulmonary aspergillosis (ABPA) in approximately 2% to 7.8% of patients with CF [87,88]. Aspergilloma or invasive aspergillosis is rare [89,90].

Respiratory viruses have been recognized since the early 1980s in CF. Respiratory viral disease can be more severe in patients with CF than non-patients with CF and can contribute to the progression of lung disease [91–96]. RSV infections have been shown to be associated with a rise of *P. aeruginosa* antibodies in patients who harboured these bacteria [97]. RSV can cause severe acute illness in patients with CF and persistent morbidity [92,96]. Influenza infection has also been associated with respiratory deterioration and increased hospitalization among patients with CF [94,98,99]. Adenovirus, rhinovirus and parainfluenza viruses have been associated with respiratory illness [92,96]. The impact of rhinoviruses on patients with CF is unclear at present. There is some evidence that viral respiratory infections predispose the CF lung to bacterial infection [95,96,100].

5.2. Bacterial factors which inhibit eradication

Most initial *P. aeruginosa* are nonmucoid, and in general completely susceptible to pseudomonal-specific antibiotics when they are contracted from the environment. In addition, plug formation and, hence, sputum production is often minimal when *P. aeruginosa* is only colonizing the airways. Therefore, early treatment of *P. aeruginosa* (shortly after assessment of *P. aeruginosa* lung colonization) may preserve lung function [101–103] and lead to eradication of the pathogen [103–105]. However, without treatment, this pathogen often persists in the CF airway.

Accumulated evidence since the 1960s indicates that mucoid *P. aeruginosa* phenotypes originate from the nonmucoid colonising strain by a variety of genetic, environmental and selective influences including mutation [106] and growth in viscous anaerobic/microaerobic mucus [107]. In addition, other mechanisms for this phenotypic switch have been demonstrated in vitro [108]. Oxygen limitation and low metabolic activity in the interior of the bacterial biofilm correlate with poor antibiotic activity against biofilm bacteria [109]. The exact time period in which *P. aeruginosa* adapts to the CF lung by switching to mucoidy is not known. However, in one episode where it was possible to accurately document acquisition of environmental *P. aeruginosa* from a hydrotherapy pool, mucoidy was detected within 3 months [110]. Mucoid *P. aeruginosa* phenotypes carrying mutations in alginate repressor genes are uniformly present in chronic infection; however nonmucoid variants can also be found [60], representing the original colonising strain or nonmucoid revertants arising from mutations in alginate structural or regulatory genes [106]. These factors including (1) alginate production leading to a mucoid colonial morphotype in vitro or (2) antibiotic resistant bacterial phenotypes, (3) lung abcesses, and (4) airway mucus plug formation impede the eradication of pathogens from CF airways by antibiotic therapy.

Mucoidy of *S. aureus* in CF airways [111] is also triggered by anaerobic conditions [112]. Furthermore, NTM, which may be found in sputum specimens of patients with CF, have the ability to form biofilms [113] as do *S. maltophilia* and *A. xylosoxidans*. Mucoid *P. aeruginosa* and possibly also mucoid *S. aureus* restrict the penetration of most antibiotics, particularly the penetration of aminoglycosides and two to three orders of magnitude higher tobramycin concentrations are needed to be comparably effective against *P. aeruginosa* biofilms compared with its nonmucoid variant [114].

However, non-mucoid *P. aeruginosa* can be more resistant to antibiotics than their mucoid variants [115]. Thus, for many reasons, antibiotic therapy for chronic bacterial lung infections in patients with CF generally only achieves a reduction of *P. aeruginosa* colony counts rather than complete eradication. Due to the stresses imposed by the host defense system and by repeated antibiotic treatments, hypermutable strains of *P. aeruginosa* develop in CF airways [116,117], and result in rapid antibiotic resistance thus contributing to the impairment of bacterial eradication. In general, during the chronic course of the infection, *P. aeruginosa* colonies become increasingly resistant to antimicrobial agents making therapy progressively less effective.

Finally, negatively charged glycoproteins and human DNA in plugs formed as a consequence of neutrophil influx and decay may restrict bacterial clearance. Plugs may bind positively charged aminoglycosides such as tobramycin [118] and cause obstruction. With the exception of *B. cepacia* complex, *P. aeruginosa* is thought to trigger more obstruction/inflammation than the other CF-related pathogens.

5.3. Eradication trials of P. aeruginosa and S. aureus

The initial report of the feasibility of reducing both the number of *P. aeruginosa* organisms isolated and also the frequency of isolation from the respiratory tract cultures of the treated patients by using nebulised colistin for early *P. aeruginosa* colonisation [119] was confirmed in an single-blinded, controlled, randomized study, using combined treatment with aerosolized colistin and oral ciprofloxacin. This significantly reduced the onset of chronic *P. aeruginosa* infection in treated patients with CF compared to untreated controls [104]. Similarly, a placebo controlled double-blinded, randomized tobramycin inhalation study showed that after onset of *P. aeruginosa* infection, the time of conversion to a *P. aeruginosa* negative respiratory culture was significantly shortened by active treatment, suggesting that early tobramycin inhalation may prevent *P. aeruginosa* pulmonary infection in CF [105]. A follow-up study using historical controls [101] demonstrated that aggressive treatment prevented or delayed chronic *P. aeruginosa* infection in 78% of the patients with CF for 3.5 years. After introduction of early intensive antibiotic treatment, the probability of still not having developed chronic *P. aeruginosa* infection 7 years after the first isolation of *P. aeruginosa* was above 80% [120]. Furthermore, aggressive treatment maintained or increased pulmonary function during the year after inclusion compared with the historical control group, in which pulmonary function declined [101]. Data from three subsequent studies also demonstrate that early treatment of *P. aeruginosa* lung colonization effectively eradicates the pathogen [103,121,122]. Unpublished data from Italy reveal that their patients with CF may remain free of *P. aeruginosa* for a mean of 2.4 years using colistin in combination with ciprofloxacin (Taccetti et al., unpublished data). Other investigators have determined a median time to re-infection after eradication of 8 ± 5.7 months [123]. In order that antibiotic therapy may be initiated early enough, before established chronic infection, it is recommended that a respiratory tract culture be performed at least quarterly, preferably every month, and at any exacerbation of respiratory symptoms [5]. Although it may be thought that the increased frequency

of respiratory tract culturing in patients with CF increases the cost of care, the opposite is the case. Early antibiotic eradication therapy is much less costly than maintainance therapy for chronic *P. aeruginosa* lung infection ([124]; Taccetti et al., unpublished data).

A major difficulty in relation to early therapy is obtaining the scientific proof that *P. aeruginosa* is actually eradicated from the lungs. Negative or decreasing serum antibody titers [103], genotyping of *P. aeruginosa* [123] isolated at the next episode of bacterial lung colonization revealing a different bacterial genotype, and negative brochoalveolar lavage is supportive evidence that eradication was achieved. The recommended drugs and doses for early anti-pseudomonal therapy in CF are given in Table 2. For some patients with CF, it may not be possible to eradicate pathogens from their airways for several reasons including that they attend the CF centre only infrequently and consequently chronic infection and biofilm formation become established before treatment is initiated. Currently, a multicentre trial on *P. aeruginosa* eradication therapy in Europe is carried out using preservative free tobramycin.

Many patients with CF are initially infected with *S. aureus*. There is general agreement to treat such patients with anti-staphylococcal antibiotics for 2 to 4 weeks [1,125]. This may eradicate the organism [126,127]. In culture positive patients, anti-staphylo-coccal treatment for at least 2 weeks results in an eradication rate of ~ 75% and only a few patients harbour *S. aureus* for more than 6 months thereafter [127]. In another study, 57% to 21% of colonized/infected individuals still harboured the same *S. aureus* genotype when checked after 3 and 19 months, respectively [126]. *S. aureus* may persist intracellularly as small colony variants; these variants are often missed on routine cultures and may revert to normal strains after cessation of antibiotic treatment [34]. Whether the occurrence of MRSA will lead to a change of this epidemiological picture is not clear. If short-term courses of anti-staphylococcal therapy fail, longer treatment courses (1–3 months) are necessary [60]. The recommended drugs and doses for anti-staphylococcal therapy in CF are given in Table 3. In patients with CF infected with *H. influenzae*, recommended eradication therapy is 2–4-week courses using specific antibiotics as listed in Table 4.

Table 2
Recommended drugs and doses for early anti-pseudomonal therapy in CF

Antibiotic	Route of administration	Dose	Number of administrations per day
Ciprofloxacin	p.o.	20–30 mg/kg	2
Colistin	inhaled[a]	2–3 Million U[b]	2–3
Tobramycin	inhaled[a]	80–300 mg[c]	2

[a] Provided that the inhalation technique is effective and mouthpiece is used.
[b] 1 mg colistin base = 30.000 units.
[c] Preferably preservative free tobramycin, such as TOBI.

Table 3
Recommended drugs and doses for anti-staphylococcal therapy in CF[a]

Antibiotic	Route of administration	Dose (mg/kg/day)	Number of daily administrations
Flucloxacillin	oral	100	3
Dicloxacillin	oral, i.v.	50	3–4
Fusidic acid	oral, i.v.	25–50	2–3
Clindamycin	oral, i.v.	20–40	2–4
Rifampicin	oral, i.v.	15	2
Vancomycin	i.v.	40	2
Teicoplanin	i.v.	10	1
Linezolid	oral, i.v.(< 5 years)	10	3
Linezolid	oral, i.v.(>5 years)	20	2
Moxifloxacin	oral, i.v.(adults)	5–10	1

[a] Combination therapy is recommended using dicloxacillin + fusidic acid or dicloxacillin + clindamycin. For pathogens difficult to treat such as MRSA, rifampicin + fusidic acid or rifampicin + clindamycin can be used. Linezolid is an expensive drug and clinical experience is limited. It should also be used in combination with another drug due to the risk of development of resistance. Other drugs listed should be used for combination therapy of MRSA. Probenecid 15 mg/kg orally is recommended to delay the renal excretion of β-lactam antibiotics.

5.4. Management of chronic bacterial and fungal lung infection

The optimal management of chronic *P. aeruginosa* lung infections in patients with CF has been outlined recently [5,6]. Briefly, due to the endobronchial location of the *P. aeruginosa* infection in patients with CF and the inaccessibility of mucoid *P. aeruginosa* in plugs, high doses of intravenous antibiotics are recommended. To reach high airway concentrations, colistin or aminoglycosides are generally administered by inhalation for maintenance therapy. During acute exacerbations, intravenous application is preferred. Penicillins, cephalosporins, monobactams, carbapenems, aminoglycosides and sometimes colistin are administered intravenously (for other classes of antibiotics, see Ref. [5]). Since patients with CF are treated with antibiotics for most of their lives, monitoring for side effects

Table 4
Recommended antibiotics for eradication therapy against *Haemophilus influenzae* in patients with CF

Antibiotic	Route of administration	Dose (mg/kg/day)	Number of daily administrations
Amoxicillin	oral	50–100	3
Pivampicillin	oral	35	
Amoxicillin/	oral	50–100	
clavulanic acid		12.5–25	3
Ciprofloxacin	oral	20–30	2
Rifampicin[a]	oral	15	2
Cefuroximeaxetil	oral	20–30	2
Azithromycin	oral	10	1
Clarithromycin	oral	15	2

Probenecid 15 mg/kg orally is recommended to delay the renal excretion of β-lactam antibiotics
[a] Only in combination with other antibiotics due to high risk of development of resistance.

of antibiotic therapy should be carried out regularly. When antibiotic therapy is started before susceptibility patterns are available, the therapy has to be adjusted accordingly when no clinical improvement is achieved. Whether patients with CF should be treated for prolonged periods of time with antibiotics to which *P. aeruginosa* is resistant remains unclear. Due to an increase in antibiotic resistance of *P. aeruginosa* strains after inhaled tobramycin therapy, an intermittent regimen is currently used. To avoid or postpone antibiotic resistance and for synergy reasons [5], combination therapy is widely used in patients with CF.

Major problems for optimal antibiotic therapy are *B. cepacia* complex, *S. maltophilia* and *A. xyloxidans* all of which are usually inherently multiresistant. With these pathogens, combination therapy with antibiotics, shown to be active as single agents in vitro, should be used in 2–4-week courses (Table 5). However, more studies are needed to further optimize therapy.

The treatment of ABPA relies on steroids such as prednisone. The role of concomitant anti-fungal therapy such as itraconazole, voriconazole, caspofungin or liposomal amphoreticin [128] is presently unclear, although clinical and serological effects have been observed [129]. Therapeutic trials for respiratory virus infections in patients with CF have not been performed and prevention by vaccination is regarded as important.

Table 5
Recommended antibiotics for therapy against *B. cepacia* complex, *S. maltophilia* and *A. xyloxidans* in patients with CF[a]

Antibiotic	Route of administration	Dose (mg/kg/day)	Number of daily administrations
Doxycyclin	oral	2–3	1
Sulfamethoxazol/ trimetoprim	oral/i.v.	50–100 + 10–20	2–4
Ceftazidime	i.v./inhal	150–200	3
Meropenem	i.v.	120	3
Colistin[b]	i.v.[c]	2–5	2–4
Tobramycin	i.v.[c]	5–10	1–2
Ciprofloxacin	oral/i.v.	20–30	2–3
Moxifloxacin	oral/i.v.[d]	5–10	1
Amoxicillin/ clavulanic acid	oral/i.v.	50–100/ 12.5–25	3
Aztreonam	i.v.	150–250	3[e]
Ticarcillin/ clavulanic acid	i.v.	200–300/ 6–10	4–6[e]
Piperacillin/ tazobactam	i.v.	200–240/ 25–30	3–4

[a] These species are resistant to many antibiotics and easily become resistant to antibiotics during treatment. Susceptibility testing must therefore guide the choice of antibiotics and combination therapy is usually recommended (for *B. cepacia complex*, three i.v. drugs are recommended). Probenecid 15 mg/kg orally is recommended to delay the renal excretion of β-lactam antibiotics.

[b] *B. cepacia complex* is always resistant to colistin.

[c] Recommended doses for inhalation, see Table 2.

[d] For adults.

[e] *Aztreonam/ticarcillin/clavulanic acid* combination therapy because of synergism against *S. maltophilia*.

5.5. Prophylactic antibiotic treatment

The use of prophylactic antibiotics in an attempt to prevent infection has been suggested, since lung infections with other microorganisms including viruses may pave the way for *P. aeruginosa* acquisition. On the other hand, it is thought that an increased incidence of *P. aeruginosa* may result from frequent use of antibiotics, since broad spectrum antibiotics, in particular, may depress the normal pharyngeal flora and lower the resistance to Gram-negative infection [43,130]. In the USA, *P. aeruginosa* colonized or infected the CF airway before the age of 3 years in 97% of the patients [38]. This may be primarily related to the increased innate susceptibility of the CF airway for colonisation with environmental opportunistic pathogens. Prophylactic anti-staphylococcal therapy with flucloxacillin initiated from the time of diagnosis has been assessed in a controlled study [131]. Flucloxacillin treatment resulted in a lower rate of *S. aureus* positive cultures, less cough and a lower rate of hospital admissions during the observation period. This was the only study carried out in patients diagnosed by neonatal screening, in whom treatment was probably started before the first colonisation with *P. aeruginosa.* Continuous anti-staphylococcal therapy was associated with a higher rate of *P. aeruginosa* acquisition, especially in the first 6 years of life, in a retrospective analysis [132]. However, nearly half these patients were prescribed cephalosporins. Similarly, a placebo controlled multicentre study of prophylactic cephalexin therapy from the time of diagnosis up to the age of 6 years failed to demonstrate any beneficial effect of cephalexin on pulmonary function but did lead to a higher incidence of *P. aeruginosa* in treated patients [133]. *P. aeruginosa* infection increases pulmonary inflammation and has a negative effect on morbidity and mortality, when infection persists [134]. Whether this increased risk of *P. aeruginosa* chronic infection is specific for cephalosporins or also applies to some other anti-staphylococcal agents is unclear.

6. Strategies to combat early lung inflammation in patients with CF

6.1. Causes and consequences of lung inflammation

Inflammation is present in some patients with CF from early infancy [40,135] and since untreated bacterial infections persist without antimicrobial treatment, inflammation as a response to infection persists often after the clearance of the infection [36,136]. Inflammation is detectable to a variable degree in the majority of chronically infected patients. Inflammation also increases prior to death [137]. Several hypotheses linking the basic defect in CF to bacterial lung disease have been put forward [1]. The majority of these suggest that inflammation is a consequence of infection (e.g., Ref. [39]). Due to the persisting bacterial pathogens or products, a type III hypersensitivity reaction is provoked

which is characterized by the production of specific antibodies against bacterial antigens, formation of immune complexes and the influx of neutrophils from the blood into the airway lumen [5]. The decaying neutrophils form large volume plugs leading to obstruction of CF airways. The release of high extracellular concentrations of lysosomal serine proteinases progressively impairs multiple defense pathways in addition to endobronchial tissue destruction. Chronic lung inflammation with episodes of acute exacerbations initiates several physiological and metabolic changes with deleterious effects including weight loss, anorexia, and metabolic breakdown. Cachexia, which may occur in patients with CF [136], is caused by a set of cytokines that work in concert and have multiple effects on the nutritional state of the patient [138]. Several cytokines including TNF-α, IL-1, IL-6 and IL-8 are elevated in CF BAL fluids [139]. Generally, bacterial infection and inflammation are confined to the lung. However, occasionally immune complexes may spill over to the blood stream causing arthritis and vasculitis. Whereas the lungs appear normal at birth, bacterial infection and inflammation will lead to small airway obstruction. As the disease progresses FEV_1 and vital capacity continue to fall. Decline in lung function in the later stages of CF correlates with prognosis. In chronically infected patients even with optimal therapy and between exacerbations, lung function decreases with time [36,64,140,141] and it is thought that even a small decline of 1–2% per year is deleterious in the life expectancy of the patients. To avoid the decline in lung function, regular microbiological monitoring, early intensive therapy and also perhaps anti-inflammatory therapy, is warranted.

6.2. Diagnosis and monitoring of lung inflammation

So far, it has been proposed to evaluate lung inflammation by measuring markers of inflammation in the blood and/or in the airways, and also to use lung function measurements, chest radiographs as well as High Resolution CT (HRCT) scan. However, the investigation of inflammatory markers in the patient sera, such as C-Reactive Protein (CRP), neutrophil elastase-alpha-1-antitrypsin complex [142], and cytokines, may not reflect the inflammatory status in the airways. In addition, lung function tests, chest x-rays and HRCT scans are only indirectly indicative of lung inflammation. HRCT scan may already show localized signs of destruction as a consequence of inflammation when lung function measurements still are normal [143]. Regular recording of lung function at close intervals using sensitive techniques in both children and adults is the most valid measure to detect lower airway inflammation. BAL has been used for these purposes [36,134,139,144,145]. The presence of high concentrations of neutrophil enzymes including elastase (NE) and myeloperoxidase (MPO) [135,140], high cytokine levels [144,145] and an imbalance of serine proteases and serine protease inhibitors [135] has been demonstrated, and oxygen radical damage of the lung tissue is also present in CF infants [146]. A major disadvantage of BAL is undoubtedly the invasive nature of the procedure limiting sequential investigations. Therefore, the collection of exhaled breath condensates (EBC) has been suggested to detect and monitor the course of inflammatory markers in CF and other airways diseases [147]. Volatile compounds such as hydrogen peroxide (H_2O_2) [148], nitric oxide [149], 8-isoprostane [150] and isoprene [151] have been measured in EBC from CF and other patients. However, whether these markers of inflammation can be used to monitor anti-inflammatory therapy in CF is still questionable.

6.3. Anti-inflammatory treatment strategies

Several anti-inflammatory drugs have been tested in patients with CF during the last two decades (reviewed in Ref. [5]). These include corticosteroids such as prednisone [152], which were associated with considerable side effects when given at high doses for prolonged periods of time [153] including a risk of persistent growth impairment [154]. Corticosteroids are still the treatment of choice for ABPA and short-term oral courses have demonstrated an increase in lung function and decrease serum IgG and cytokine concentrations [155]. The administration of inhaled corticosteroids which may prevent side effects of this class of drugs was efficient in a 3 months study [156], but larger multicentre trials with higher doses given for a longer time are needed [157–159] before their benefit may be definitively proven. The concomitant use of budesonide and itraconazol, however, may induce iatrogenic adrenal insufficiency [160] and Cushing's syndrome has also been observed [161]. From the various non-steroidal anti-inflammatory drugs, ibuprofen [162,163] has been successfully evaluated in a large CF study. Its beneficial effect on lung function is particularly evident in patients <13 years. The LTB_4-receptor antagonist BIIL 284 [164] is currently being tested in a multi-national CF study. While animal studies suggest beneficial effects of recombinant IFN-γ [165,166], studies in patients with CF with this drug are lacking.

Protease inhibitors such as recombinant secretory leukocyte protease inhibitor (SLPI) have been tested in patients with CF. rSLPI aerosol therapy in patients with CF caused a marked reduction in IL-8 levels in the epithelial lining fluid [167], however, high concentrations have to be given [168]. While a trial with aerosolized α_1-PI in a small number of patients with CF revealed promising results [169], larger studies using human plasma derived α_1-PI or transgenic α_1-PI [170] have not been published until now. In addition to specific anti-inflammatory drugs, antibiotics such as macrolides may induce anti-inflammatory effects and have improved lung function in CF adults and children with chronic *P. aeruginosa* infection [171,172]. Long-term, low-dose administration of macrolide antibiotics has been associated with down-regulation of nonspecific host inflammatory response to injury and promotion of tissue repair [173].

The obstruction present in infected/inflamed CF airways inhibits the activity of antibiotic and other aerosolised drugs [118,174]. Consequently, it has been suggested that antibiotic aerosolization should be preceded by physiotherapy, bronchodilatators and mucolytic agents such as recombinant human deoxyribonuclease (rhDNase) I.

When the sulphur bridges dissolving drug *N*-acetyl-cysteine has been tested in patients with CF, no major significant effect on lung function or other clinical parameters was observed [175]. RhDNase has been shown to solubilize CF sputum [176] and to be clinically effective [177]. A multinational double-blind study in 968 adults and children with CF showed that rhDNase reduced the number of exacerbations of pulmonary symptoms, improved lung function and was well tolerated [178]. A second multi-national, open-label study conducted in 974 patients with CF with moderate lung disease demonstrated that administration of rhDNase was safe, well tolerated, and effective under conditions reflecting routine clinical practice in patients with CF [179]. Treatment of young patients with CF with rhDNase maintained lung function and reduced the risk of exacerbations over a 96-week period [141]. In the light of biofilm producing microorganisms such as *P. aeruginosa* or *S. aureus*, the observation that rhDNase also solubilizes biofilms is interesting [180]. Furthermore, infection rates have been shown to be significantly decreased in a rhDNase treated group of patients with CF compared to controls [181].

However, some mucolytic drugs may adversely influence the activity of antibiotics [182]. In vitro, binding of tobramycin to components of CF sputum in vitro was increased after rhDNase, although bactericidal activity of sputum dialysate was not altered [183]. On the other hand, it has been proposed that rhDNase can promote mixing of bacteria, antimicrobial agent and sputum [184] and improve gene transfer [185–187] by improving penetration through sputum. It has been suggested that rhDNase may liberate cationic mediators such as neutrophil elastase bound to DNA in the airways [188,189] and hypertonic saline may potentiate neutrophilic inflammation. However, this hypothesis has not been confirmed in clinical studies [190–192]. Hypertonic saline has been shown to improve mucociliary clearance in patients with CF [193] and the clinical effects compare unfavourably with rhDNase [194]. No clinical benefit of hypertonic saline was observed during a long-term randomized controlled trial [194].

7. Non-pharmacological interventions and application of hygienic principles to prevent lung disease in patients with CF

7.1. Reservoirs and routes of transmission of bacterial pathogens

S. aureus colonizes the skin including the anterior nares of approximately 30% of healthy individuals. Thus, transmission from healthy carriers to patients with CF most probably via hand contacts is an important route. Nasal and lung-infecting isolates typically have an identical genotype [126,195]. Transmission of *S. aureus* within CF and non-CF families is regularly observed [126]. Chronically infected patients with CF generally harbour the same clone of *S. aureus* for at least 1 to 2 years [126,196]. Healthcare-associated transmission of MRSA from non-CF to patients with CF and from CF patient to CF patient has been reported and may be facilitated by hospitalization of patients with CF on general pediatric or adult medical wards [197,198].

P. aeruginosa has been repeatedly isolated from soil, plants and vegetables [199]. It is a salt-sensitive water organism often recovered from polluted water sources, seawater near sewage outfalls, hospital sink drains, toilets and showers, dental equipment, ineffectively chlorinated swimming pools and whirlpools, air humidifiers, sanitary plumbing, and many medical devices and equipment which contain water (for review, see Ref. [200]). *P. aeruginosa* is sensitive to desiccation and light and hence short-lived in aerosols and on dry surfaces [201]. However, *P. aeruginosa* may survive considerably longer in the presence of protein and other organic material, e.g., sputum [202,203]. Heating to 70 °C destroys *P. aeruginosa.* Most individuals with intact body surfaces and flora are resistant to *P. aeruginosa* colonization [199]. However, antibiotic treatment may increase human gut colonization with *P. aeruginosa* [204].

P. aeruginosa aerosols may be generated from some contaminated reservoirs such as nebulizers, toilets, sink drains, non touch taps and dental equipment, leading to acquisition by patients with CF [201,205–210]. Close contact with such contaminated reservoirs seems to be important for the transmission of pathogens via aerosols, since survival of *P. aeruginosa* in aerosols is restricted to a few minutes. The microbial burden is highest the first time when water is run or toilets are flushed in the morning probably due to overnight multiplication of sink bacteria [201]. The high identity of patient and sink strains in some studies is also suggestive that sink strains may colonize patients or vice versa [202,211–213]. Whirlpools and hot tubs frequently harbour *P. aeruginosa* and thus present a high risk for CF individuals [214,215]. Infection of patients with CF from a hospital hydrotherapy pool has been described [214]. Swimming pools, if correctly managed and disinfected by chlorine, are free of or contain very little *P. aeruginosa* and therefore are regarded as not hazardous. However, plastic animals used in swimming pools may be contaminated with *P. aeruginosa* [216]. Water containing tubing in dentist's equipment may also be contaminated with *P. aeruginosa* [209,217–219].

P. aeruginosa can be detected from many sources in CF centres [203,220] including hands of healthcare workers (HCWs) and patients and in the air around patients with CF during coughing [60,202,203,220,221]. Ingestion of *P. aeruginosa*-contaminated food [222] may lead to colonization of the oropharynx or colonization of the gastrointestinal

tract. In animal experiments, the addition of penicillin to drinking water leads to intestinal colonization by *P. aeruginosa* [204]. The use of antibiotics in hospitalized patients may thus increase the incidence of *P. aeruginosa*-positive stools. Whether such a mechanism led to an increased *P. aeruginosa* acquisition rate in patients attending the multicentre cephalexin trial is not known [133]. An important human reservoir for *P. aeruginosa* is the chronically infected CF patient (see cross-infection).

B. cepacia complex bacteria are well-known soil and plant microorganisms [199,223], but their distribution in different natural habitats is poorly documented. This is primarily due to the lack of sufficiently selective isolation media, but also to the poor sensitivity of some of the currently used selective media, to the initial slow growth of *B. cepacia* complex bacteria upon these media, and to the use of inadequate identification procedures. As a consequence, there are few reports on their environmental distribution [199,224–226]. Nevertheless, all *B. cepacia* complex bacteria have been recovered from soil and water samples [69] and the emergence of newly infected patients carrying strains characterized by unique genomic fingerprints convincingly suggests that environmental acquisition must occur. In addition, cross-infection among CF individuals has been reported numerous times [227–231], An epidemic *B. cenocepacia* (genomovar III) strain that colonises over 200 patients with CF in 31 cities in 24 states of the USA has been identified from agricultural soil [232,233].

Similarly, a variety of genome-based typing systems showed that a *B cepacia* genomovar I strain was clonal with an isolate recovered from a CF patient [234]. The use of *B. cepacia complex* in agriculture poses a threat to patients with CF [223,234,235]. The organism was also isolated from sinks and refrigerators in homes of patients with CF and healthy families [236] and in hospital sinks (Döring, unpublished). *B. cepacia complex* contamination of both respiratory therapy equipment [237], antiseptics and disinfectants [238] has also been demonstrated. *B. cepacia* complex is not found in healthy individuals [239]. Like *P. aeruginosa* [202], *B. cepacia* complex embedded in sputum has prolonged survival on surfaces [240]. Whether airborne transmission of *B. cepacia* complex via coughing of infected patients occurs is unclear [241]. Misidentification of a range of Gram-negative non-fermenters including *A. xylosoxidans, S. maltophilia* and *B. cepacia* complex is especially problematic and presents a challenge to effective infection control in CF [69,242,243].

S. maltophilia is a typical water organism found in tap water or water in dentist tubes [209,244]. Similarly, *A. xylosoxidans* is found in water reservoirs [245]. Genotyping of *S. maltophilia* and *Achromobacter* species in CF centres has not yet indicated transmissability as a major problem [79,246–248]. Although similar results have been published for *A. xylosoxidans* [79], in two other studies one or more patient pairs shared a single genotype of *A. xylosoxidans* [249]. Well-designed epidemiologic studies on routes of transmission are needed.

NTM are also found in several water reservoirs including dental unit waterlines [250]. In patients with CF, multiple nosocomial outbreaks of NTM have been reported due to either inadequate disinfection/sterilization of medical devices or environmental contamination of medications or medical devices [251]. Person-to-person transmission of NTM has not been described except via inadequately cleaned and disinfected medical devices [251,252]. Several studies indicate that patients with CF may be infected with these pathogens [80,85,253,254]. Antibiotic therapy has been suggested to be a risk factor for NTM colonization/infection in patients with CF [255].

Infections of patients with CF with ubiquitous *Aspergillus* spp. from many environmental sources may be the consequence of antibiotic therapy [35,256]. Fungal spores may become aerosolized within hospitals particularly during reconstruction [257,258].

Respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus and rhinoviruses are the most common viruses of the respiratory tract and are transmitted primarily via direct contact with infected persons or aerosolization of infective droplets. Viral particles are introduced through the mucous membranes of the eyes and nose of susceptible individuals. There are no CF-specific transmission issues.

Unravelling transmission routes of microorganims is generally difficult, since multiple routes are possible; these include (1) direct patient-to-patient contact, (2) contacts between patients and healthy carriers of the bacteria (e.g., hospital personnel) who acquired colonization from other patients or from the environment, and (3) direct contact between the patient and the environmental sources. Identification of sources, typing of the microorganism in question and case-control studies are used to investigate the epidemiology of a transmission route [259].

Most individual patients with CF retain the same clone of *P. aeruginosa* throughout their lifetime [260,261] and cross-infection can be demonstrated, especially between siblings. However, the initial source of *P. aeruginosa* for most patients remains unknown.

Reliable and highly discriminatory typing methods are essential to any microbiological surveillance programme or investigation of transmission routes. Since bacterial strains may undergo substantial phenotypic changes during the course of chronic infection in patients with CF (e.g., Refs. [106,111,261,262]) most bacterial organisms today are typed employing genetic methods. ‘Finger-printing’’ of chromosomal DNA using pulsed field gel electrophoresis (PFGE) or random amplified polymorphic DNA analysis (RAPD) are often used [125,202,243,261,263–266]. Reference laboratories are essential to assure the quality standards for species identification and strain typing and to perform techniques not available at local level. Reference laboratories also facilitate the identification of the spread of epidemic strains at national and international levels.

7.2. Cross-infection

The expression "cross-infection" is often used to describe outbreaks of infections with a single strain, implicating person-to-person transmission or acquisition from a common contaminated source. In this sense, cross-infection can result from a mechanism by which an infected patient or a healthy individual contaminated with an opportunistic or pathogenic microorganism transfers this microorganism to another non-infected patient. Due to its presence on human epithelia, transmission of *S. aureus* within CF and non-CF families is regularly observed [126,267]. Healthcare-associated transmission of MRSA from non-CF to patients with CF and from patients with CF to patients with CF has been reported [197,198].

Many epidemiological studies using typing methods demonstrate cross-infection between patients with CF with *P. aeruginosa* [202,268–274]. Evidence for cross-infection also comes from the observation that CF siblings often harbour genotypically identical strains [271]. Hospital staff and the air [221] may act as a vehicle of *P. aeruginosa* transmission to patients with CF in the hospitals [201,202,275]. Cross-infection has also been shown to occur in summer camps between patients with CF [263,271,276]. High prevalence of *P. aeruginosa* infection makes cross-infection much more likely to occur than with other CF related, prevalent pathogens as indicated by mathematical models [269]. The exact transmission routes, however, have not been detected and cross-infection has also not been detected in some centres [277]. Whether these discrepancies reflect strain-specific characteristics, centre differences regarding conditions for cross-infection including the size of the centre and the opportunities for contact between patients with CF, is uncertain.

Like *P. aeruginosa,* several studies using genotyping methods have shown the transmission of *B. cepacia* complex from patient to patient in both healthcare and non-healthcare settings [110,227,229,230,278–281]. Transmission is facilitated by prolonged direct or indirect contact. Infected patients with CF may cough and thus create bacterial contaminated aerosols, which then may colonize other patients [282]. However, such a transmission route was not supported in other studies [202,283]. *B. cepacia* complex strains may remain endemic in CF treatment centres or outside hospital settings for many years [284]. Epidemic outbreaks of the same *B.cepacia* complex in different CF centres have been traced to traveling patients with CF [285,286].

There is limited evidence for cross-infection of other CF related pathogens [287].

7.3. Prevention of cross-infection

If guidelines for infection control are followed including separation of infected patients from uninfected, susceptible patients and the implementation of hygienic measures, prevention of cross-infection has been demonstrated. Based on mathematical models [120], the risk for cross-infection increases with increasing numbers of patients attending the CF centre. In addition, it increases with the contact density between infected and non-infected patients and if the prevalence of infected patients is >20%. Therefore, smaller centres with low prevalence of infected patients and where the contact density is low may not have detectable cross-infection, whereas larger centres with high prevalence of infected patients and with high contact density may experience such cross-infection more often. To prevent cross-infection, particularly in larger centres, regular culturing of CF related pathogens, calculation of incidence rates and bacterial typing are demanded. If incidence rates are high or increasing, and typing suggests spread, analysis of possible sources and routes of cross-infection is required, followed by the implementation of appropriate infection control methods.

Segregation of patients has been shown in several CF centres to prevent cross-infection with *P. aeruginosa*. For instance, whereas a cohort of 22 patients with CF shared the same *P. aeruginosa* clone, probably acquired nosocomially, none of the 24 patients with CF of another cohort who had been segregated for eight years, acquired this clone [274]. By segregating patients with CF, an epidemic of a multiple antibiotic resistant strain of *P. aeruginosa* was stopped [120]. Similarly, an early *B. cepacia* complex epidemic was stopped segregating patients with CF [288]. On the other hand, centres that have failed to practice segregation have documented on-going transmission of epidemic clones [284,289]. Due to the accumulated evidence of cross-infection between patients with CF, the attendance of patients with CF at summer camps and other social events has been discouraged. However, this recommendation is not universally supported [290]. To reduce the rate of cross-infection in hospitals, in some centres patients with CF are forced to wear surgical masks, however, there is currently no evidence has been presented that this measure is effective. Hygienic measures to decontaminate environmental reservoirs of *P. aeruginosa* including nebulizers and other medical equipment, sinks, toilets and dental tubings, have been recommended [201] and some of these have been shown to be efficient [291]. Hand disinfection for patients with CF and hospital personnel has been stressed [6,200]. The use of waterless antiseptic hand rubs is more effective than handwashing using water and plain or antimicrobial-containing soap [292]. Unfortunately, adherence by HCWs to recommended practices is low [268] and specific educational programs with active support of healthcare administrators are needed to overcome barriers to adherence with infection control guidelines at CF centres. For home therapy, patient guidelines concerning hygiene and physiotherapy need to be established [207] including monitoring of the necessary equipment. A number of guidelines and consensus reports for effective infection control programs have been published [5,6,55,293].

Table 6
Hygienic measures to prevent cross-infection in patients with CF

(1) Establishing separate cohorts inside and outside of the hospital.
(2) Implementing hygienic measures e.g.:
Hand hygiene of patients, staff, visitors
prohibition of sharing nebulizers, tooth-brushes, drinking glasses, etc.
appropriate disposal of contaminated articles
cleaning followed by sterilization or high-level disinfection of non disposable equipment including nebulizers
sink disinfection using heating devices in hospitals
daily cleaning of patient's room by disinfecting soaps

S. aureus cross-infection in non-patients with CF may be prevented by mupirocin [294]. Table 6 lists hygienic measures to prevent cross-infection in patients with CF and Tables 7a and 7b, the principles of patient-cohorting.

7.4. Physiotherapy and physical activity/exercise

Modern physiotherapy (PT) in CF consists of an individually tailored regimen incorporating inhalation therapy [5,295,296], airway clearance and physical exercise [297]. The components and dosage (duration and number of treatments per day) of the individualized therapeutic regimen will differ according to the state of the patient. During acute exacerbations the regimen may be more complex and intensified compared to baseline maintenance PT therapy. The timing of the different parts of the PT package in relation to each other, to meals and daily routines is essential in achieving optimal treatment with minimal side effects. Ongoing patient education, regular patient/physiotherapist communication and assessment, adherence with quality treatment and early identification of exacerbations are critical. Selection of the components of the regimen is made up of cooperation with the patient/family taking into account pulmonary pathophysiology, age, social, economic, cultural, lifestyle considerations and personal choice to optimize quality of treatment and adherence.

PT is not only rehabilitative but rather aims to remove viscous airway secretions thus compensating for impaired mucociliary clearance and minimizing the lung disease process [298,299]. Many different types of PT are practised around the world with asymptomatic and symptomatic infants, however, few of these techniques are evidence based [300]. The assessment of any impact of physiotherapy on lung disease is difficult in long-term studies, since other treatment strategies of the care package are constantly applied and developed continuously. Therefore, randomized controlled trials assessing the effects of PT versus no PT on patients with CF have not been performed [301]. Conclusions concerning the efficacy of physical training in CF are limited by the small number of randomized controlled trials and the fact that physical training is already part of standard treatment [302]. Since daily PT requires much discipline from patients and parents and may adversely affect the relationship between parents and child randomized trials to assess the preventive effect of physiotherapy are urgently needed. Particularly, there is a need to assess the preventative effect of physiotherapy on the development of mucus

Table 7b
Practical aspects of cohorting patients with and without *P. aeruginosa* and *B. cepacia* complex

Wards	#1	#2	#3: single cubicles
No P.a./Bc	+		
Intermittent P.a.	+		
Chronic P.a., sensitive to antibiotics	(+)[a]		+[a]
Chronic P.a., multiresistant		+	
Intermittent/ chronic Bc			+

Outpatient clinic	Monday	Tuesday	Wednesday	Thursday	Friday
No P.a./Bc	+	+	+		
Intermittent P.a.	+	+	+		
Chronic P.a., sensitive					+
Chronic P.a., multiresistant				+	

Intermittent/chronic Bc: Isolation room with separate waiting room and entrance-cleaned after each patient.

[a] Patients without P.a. can be admitted to ward #1 at the same time as patients with intermittent P.a. provided that the latter are on prolonged anti-P.a. treatment (usually inhaled colistin and ciprofloxacin or inhaled tobramycin), but they must not share rooms. Patients with chronic P.a., fully sensitive to antibiotics can be admitted to ward #1 provided there are no other CF patient at the same time. Otherwise, they will be admitted to ward #3 (isolation cubicles).

Table 7a
Principles of patient-cohorting

	P. aeruginosa	B. cepacia complex	MRSA	*S. maltophilia*	A. xylosoxidans	MOTT[a]
Cohorting	+	+	+	–	–	–
Number of cohorts	4[b]	*n*[c]	1			
Universal hygienic precautions	+	+	+	+	+	+
Wards	+	+	+	–	–	–
Outpatient clinic	+	+	+	–	–	–

[a] Mycobacteria other than tuberculosis.

[b] No *P. aeruginosa*, intermittent *P. aeruginosa* colonization, chronic *P. aeruginosa* infection with sensitive strains of *P. aeruginosa*, chronic infection with multiply resistant strains of *P. aeruginosa*.

[c] Each patient is isolated in a single cubicle.

plugging of the airways, micro-atelectasis, anaerobic/hypoxic environment [107,109] and early HRCT signs of lung destruction [143] in infants.

Support for PT is derived from a study showing that a 3-week period without PT led to a worsening in lung function status [303]. Combining IV antibiotic treatment with intensified airway clearance has been shown to improve lung function more than IV antibiotic treatment alone [304]. Although it has been suggested that very young CF infants should receive the full range of PT treatments as applied in older patients [305], differences concerning anatomy, physiology, gastro-oesophageal function and respiratory behaviour between very young infants and adults with CF demand more specific strategies [306]. A higher gastro-oesophageal reflux (GOR) index and longer reflux episodes have been demonstrated in *P. aeruginosa*-infected versus non-infected infants [307]. Since certain airway clearance techniques including positioning and manual techniques are thought by some to provoke episodes of GOR [308,309], it has been recommended that asymptomatic infants with CF should not be treated in head down positions [310]. However, others would contest the effect of posture on GOR [311].

The positive expiratory pressure (PEP) technique was found to be as effective as postural drainage. Parents and infants, however, preferred the PEP technique [312]. Physical activities combined with assisted autogenic drainage manoeuvres showed no provocation of GOR and is an alternative airway clearance technique for infants and small children [313].

Physical exercise was gradually introduced as part of the CF treatment in the late 1970s/early 1980s and collective experience from centres using it suggests beneficial effects in terms of physical capacity and function. Fragility fractures have been reported in an adult CF population [314]. Many patients showed evidence of thoracic vertebral deformity; bone mineral density was positively related to physical activity and lung function [314]. Children and adolescents with CF, despite having good lung function, have been shown to be engaged in less vigorous spontaneous physical activity than their non-CF peers [315]. Thus, physical activity/exercise, appied very early, may be beneficial. Exercise should include working capacity training, mobility exercise, muscle strengthening and stretching in order to maintain good posture and musculo-skeletal function. Chest mobility allows effective airway clearance, and good posture reduces the risk of back pain and spinal complications. Physical activity/exercise can be used as part of airway clearance.

Repeated evaluation of the different components of the physiotherapy package is essential for optimal therapy and adherence to treatment. Optimal therapy requires physiotherapists to have specialist knowledge, skills and experience of the different elements of the physiotherapy care package. Furthermore, the ability to develop good rapport, a concordant relationship with each patient and ongoing continuity of care are crucial for optimal results in the long-term.

8. Questions and answers

Answers to the following questions have been graded into categories given in Tables 8 and 9 by the participants of the conference.

(1) Heterozygote screening, prenatal screening and neonatal screening: what is recommended?

Heterozygote screening for CF, either preconceptional or prenatal has a variable and often low uptake in different countries and whole population heterozygote screening is not recommended (BIII). When prenatal heterozygote screening is offered, prenatal diagnosis should be available (AIII). When prenatal screening is carried out for other diseases, screening for CF should routinely be offered to the pregnant woman (AIII). Before offering heterozygote screening, general social and genetic counselling is needed. Neonatal screening is recommended as it offers the opportunity to prevent malnutrition and chronic respiratory infection by early interventions (AI). Also one of the main advantages of newborn screening is that it enables the parents to take informed choices about future pregnancies (AII).

(2) Does newborn screening improve patients' clinical status and does it lead to earlier intervention in patients with CF?

The clinical status of patients with CF diagnosed by neonatal screening improves nutritional and pulmonary status, provided that they receive approved standards of care (AI).

(3) What is the adequate standard of care after a CF diagnosis necessary to provide clinical benefit?

Approved standards of care are defined by international consensus groups or national consensus groups of CF specialists. Patient numbers in CF centres should be at least approximately 50 patients or more (CIII). The care should be provided by an adequately resourced multidisciplinary CF team (BIII).

(4) How does diagnosis of CF lung infection differ from that of other patients with lung disease?

CF lung disease is part of a multisystem disease and may have more severe consequences for life expectancy than other causes of lung infection. The CF lung is unique and highly susceptible to colonization/infection with a large number of unusual environmental opportunistic organisms. Specialist microbiological facilities are required for diagnosis and should be used to provide state-of-the art surveil-

Table 8
Definition of categories reflecting the scientific strength of recommendations for or against its use

Category	Definition
A*	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate good evidence to support a recommendation against use
E	Good evidence to support a recommendation against use

* From Refs. [316,317].

Table 9
Categories reflecting the quality of evidence on which recommendations are based[a]

Grade	Definition
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

[a] From Ref. [316].

lance and the microbiological data for effective cross-infection control (AII). In addition to sputum culture for bacterial pathogens, continuous, standardized antibody monitoring for *P. aeruginosa* is considered by some to be helpful (BII). Detection of any respiratory pathogens should prompt antimicrobial treatment (AII).

(5) What are the benefits of CF patient registries in Europe and how are registries implemented?

CF registries are important tools to monitor and improve standards of care (BIII). Benefits include the generation of reports to individual institutions and patients, formation of quality groups with quality ranking, learning from the best centres, recognition of alarm signals for early therapeutic intervention and the creation of decision trees. The existing national registries should unite into a European registry (BIII).

(6) What is early intervention?

If there is clinical, bacteriological or radiological evidence of infection (this includes culture of a known pathogen) or inflammation, an intervention is indicated, but a clear diagnosis cannot always be made in non-sputum producing patients (AII). Respiratory cultures should be obtained at least every 3 months or ideally every month and in the presence of any increase in respiratory symptoms (AII).

(7) How is eradication of major bacterial pathogens in CF defined, how it is achieved and how long are patients with CF free of bacterial pathogens after eradication therapy?

Since bacteria can persist in low concentrations in some of the airways, it is nearly impossible to prove eradication. Repeated negative respiratory cultures (at least three) within a 6-month period months after cessation of treatment in the presence of negative specific antibodies is practical evidence for eradication of a bacterium (BIII). There is limited information available only for different approaches to treat early *P. aeruginosa* infection and even less for most other bacteria. The duration of therapy may be important as shown for the combination of ciprofloxacin/inhaled colistin, where 3-month versus 3-week treatment was associated with an increase of the median time to recurrence/reinfection from 9 to 18 months compared with historical controls (BII). Early *P. aeruginosa* infection has been successfully eradicated with inhaled colistin or tobramycin, oral ciprofloxacin/inhaled colistin or tobramycin, intravenous treatment alone or in combination with inhaled colistin or tobramycin (AII). The optimal form of therapy is not established. In spite of early and aggressive treatment, it may not be possible to eradicate bacterial pathogens from airways of patients with CF, resulting in chronic bacterial infection. A course of anti-staphylococcal therapy for at least 2 weeks is likely to eradicate a new infection with *S. aureus* in the majority of patients. It is important to try to eradicate other pathogens such as MRSA, *B. cepacia* complex, *S. maltophilia, A. xylosoxidans* and other Gram-positive and Gram-negative bacteria using antibiotics based on individual sensitivity tests (AII).

(8) How does the bacterial phenotype influence eradication from CF airways?

Early *P. aeruginosa* colonization/infection usually occurs with non-mucoid strains that are more amenable to eradication (AI). Even early infection with mucoid *P. aeruginosa* may be eradicated in individual cases and attempt to eradicate should be made (BII). However, it is usually impossible to eradicate chronic mucoid *P. aeruginosa* infection in patients with CF because of its biofilm mode of growth. Small colony variants of *S. aureus* have also been found to be resistant to eradication.

(9) How does antibiotic resistance influence eradication from CF airways?

In the absence of cross-infection with multiresistant strains, nearly all newly detected strains of *P. aeruginosa* are sensitive to the majority of anti-pseudomonal antibiotics (AII). Therefore, resistance in early infection is less of a problem compared to chronically infected patients. Inherent resistance (in contrast to acquired resistance) remains a problem for MRSA, *B. cepacia* complex, *S. maltophilia* and *A. xylosoxidans* and this causes difficulties in eradication (AII).

(10) If eradication cannot be achieved what is the optimal management for the major bacterial pathogens in CF?

If the initial therapy for early colonization/infection does not eradicate the organism, another treatment regimen, including intravenous antibiotics should be administered (BII). It is unclear how many different treatment regimens should be used before it is considered impossible to eradicate the organism in a given patient. If the patient becomes chronically infected with *P. aeruginosa*, treatment should be given according to the previous ECFS consensus document (Döring et al. [5]) (BIII).

(11) Are prophylactic antibiotics effective to prevent bacterial lung infection?

There is some evidence that prophylactic anti-staphylococcal antibiotic treatment is effective in reducing the rate of *S. aureus* positive respiratory cultures (AI). There is also data suggesting that this form of therapy especially with oral cephalosporins may increase the risk of *P. aeruginosa* infection (AI). As the clinical benefit of long-term prophylactic anti-staphylococcal antibiotic treatment remains unproven, there is currently insufficient evidence to recommend this approach. However, there is limited evidence of benefit in the first 2 years of life (CIII). In the case of *P. aeruginosa*, there is

only one observational study on long-term prophylactic inhaled gentamicin in patients with CF to suggest that prophylactic antibiotic therapy may be effective in preventing *P. aeruginosa* colonization/infection (CII). In view of the therapeutic burden of prophylactic treatment and the evidence-based efficacy of early intervention therapy, the prophylactic approach is not currently recommended (DIII).

(12) What is the background for airway inflammation in CF, how it is defined and which markers are useful to monitor it?

Airway inflammation is an early phenomenon in CF and it is clear that the inflammatory response to microbes and other pro-inflammatory stimuli is augmented and prolonged. Airway inflammation, which is a major cause of progressive lung damage, is largely neutrophilic, with multiple complex mechanisms. At present, there are no reliable non-invasive routine markers for early inflammation, and clinicians have to rely on clinical signs and symptoms. Pseudomonas antibody levels correlate well with the severity of chronic *P. aeruginosa* infection (AIII).

(13) Which anti-inflammatory drugs are clinically effective in patients with CF?

Firstly, any underlying cause must be treated energetically (AIII). Long-term corticosteroidal drugs have proven clinical effect, but have an unacceptable profile of side effects on prolonged use (EI). There is conflicting evidence of benefit for inhaled steroids outside the context of CF complicated with asthma (CII). Macrolides appear to be safe, and improve lung function and reduce exacerbations in *P. aeruginosa*-infected patients (BI), but a relevant anti-inflammatory effect of these drugs in CF airway is unproven (BII). Ibuprofen has shown clinical benefit in one trial (AI), but there are concerns about side effects and the need for monitoring of blood levels (AII).

(14) In which age groups should anti-inflammatory drugs be applied?

There is currently no evidence to recommend preventive anti-inflammatory therapy, particularly in the early years of life. The ibuprofen study suggested increased benefit in less advanced disease, in patients who were nonetheless already chronically infected, suggesting that early anti-inflammatory therapy may be beneficial (BI). However, the risk of side effects in the well-treated child for a long period must also be considered (CIII). Effective use of proven treatments for underlying causes, in particular infection, is mandatory (AI). This involves close monitoring of young infants in particular (BII).

(15) Is early treatment with therapy aiming to improve mucociliary clearance effective in maintaining lung function?

The data suggest that introducing dornase alpha early in the disease may be beneficial (AI). Although the safety of dornase alpha has been established during 2 years' continuous treatment of children with CF, there is no longer-term safety data particularly in the context of the growing lung (BII). There is no evidence to support the use of any other mucoactive agent such as hypertonic saline or *N*-acetylcysteine in the early stages of the disease (CIII).

(16) What are the major reservoirs of CF-relevant microorganisms and which routes of transmission of bacterial pathogens to patients with CF have been determined?

For the majority of patients with CF worldwide, the source of their *P. aeruginosa* infection cannot be determined. Potential reservoirs are some natural environments, other infected patients with CF and contaminated hospital settings (AII). The relative importance of these reservoirs differs between centres. Current epidemiological data suggest that each of these reservoirs may contain CF-related pathogens which may be transmitted by one or more routes. Therefore, transmission routes are complex as given in Table 10 (AII).

(17) How is evidence obtained for a given transmission route?

Evidence is obtained by microbiological surveillance, prospective studies and genotyping of isolates from patients with CF and suspected environmental reservoirs (AI). Typing data are evaluated in conjunction with epidemiological data, which may include case-control studies, and the impact of specific infection control procedures (AI).

(18) Can cross-infection occur in patients with CF?

Yes, there is compelling evidence, that cross-infection can occur between patients with CF with regard to the *B. cepacia* complex and some strains of *P. aeruginosa*, directly or indirectly (AI). Evidence for cross-infection is limited or lacking for other CF-related pathogens (AII).

(19) How is cross-infection prevented?

Table 10
Potential reservoirs of microbial pathogens in CF and possible transmission routes

Waste water (sink drains, toilets, showers)
Seawater near sewage outfalls and polluted river outlets
Medical devices and equipment containing water including equipment for testing lung function and for inhalation therapy
Ineffectively chlorinated swimming pools and whirlpools
Air humidifiers
Tubing in dentist's units
Infected patients
Contaminated healthy individuals
Soil
Plants
Vegetables

Routes of transmission

(1) Aerosolized bacteria colonize airways directly by aspiration or indirectly via hand contamination. Note: Close contact necessary (within 1 m), short-lived bacteria in aerosols and on hands, high bacterial concentrations in environmental sources.
(2) Ingestion of contaminated food colonizes airways or gastrointestinal tract.
(3) Direct contact to contaminated healthy individuals or infected patients. Note: Increasing duration and closeness of contact increase the risk of transmission. Sputum enhances bacterial survival.
(4) Infection, or cross-infection, with *P. aeruginosa* or with *B. cepacia complex* may occur in hospitals and outside the hospital, i.e., at home, at school, during travel, in restaurants, in public places, during summer camps or other meetings.

Evidence has been obtained that cross-infection can be prevented by employing various degrees of patient segregation inside and outside hospitals as described in Table 10 (AII). Practical approaches to segregation may differ from centre to centre, however, certain minimal standards, supported by appropriate microbiological surveillance, should be implemented in the CF centres with the goal of preventing exposure of non-infected patients to patients infected with potentially contagious organisms (AII). Segregation of CF siblings from each other is not recommended, since it would interfere with normal family life (AIII). Cross-infection can also be reduced by good hygiene as described in Tables 7a and 7b (AIII). This applies to the hospital environment, the hospital staff and the patients and their relatives. Education of the staff, the patients and their relatives with regard to the need for segregation and hygiene is mandatory (AIII). The risk of cross-infection is also reduced by implementing means to reduce the prevalence of infection (AII).

(20) Is chest physiotherapy justified as part of the care package to prevent a decline in lung function?

Chest physiotherapy is justified in all CF patients starting from diagnosis of the disease, since it is the primary physical method to compensate for impaired mucociliary clearance by removing viscid and inflammatory material from the CF airway (BII). Individually tailored approaches to chest physiotherapy are needed in different age groups and for individual patients (AII).

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