

Seminar

Cystic fibrosis

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Cystic fibrosis is the most common autosomal recessive disorder in white people, with a frequency of about 1 in 2500 livebirths. Discovery of the mutated gene encoding a defective chloride channel in epithelial cells—named cystic fibrosis transmembrane conductance regulator (CFTR)—has improved our understanding of the disorder's pathophysiology and has aided diagnosis, but has shown the disease's complexity. Gene replacement therapy is still far from being used in patients with cystic fibrosis, mostly because of difficulties of targeting the appropriate cells. Life expectancy of patients with the disorder has been greatly increased over past decades because of better notions of symptomatic treatment strategies. Here, we summarise advances in understanding and treatment of cystic fibrosis, focusing on pulmonary disease, which accounts for most morbidity and deaths.

Cystic fibrosis is caused by mutations in a 230 kb gene on chromosome 7 encoding a 1480 aminoacid polypeptide, named cystic fibrosis transmembrane regulator (CFTR), which functions as a chloride channel in epithelial membranes.¹⁻⁴ Over 1000 mutations in this gene have been described so far.⁵ CFTR mutations can be grouped into six classes:⁶ (1) CFTR is not synthesised; (2) defective processing; (3) regulation; (4) conductance; (5) partly defective production or processing; or (6) defective regulation of other channels. Class 1-3 mutations are most common and are associated with pancreatic insufficiency, whereas patients with rarer class 4-6 mutations typically do not have insufficiency.⁷ The most common mutation worldwide is class 2, caused by deletion of phenylalanine at position 508 (F508del) of CFTR. Yet, its frequency varies between ethnic groups—eg, 82% of patients with cystic fibrosis have F508del in Denmark versus 32% with the mutation in Turkey.⁸

Attempts to link mutations in CFTR to severity of lung disease have not been successful.⁷ The wide phenotypic variation in patients homozygous for F508del,⁹ and differences in chloride conductance between monozygous and dizygous twins,¹⁰ suggest that environmental factors, genes other than CFTR, or both, modify development, progression, and disease severity of cystic fibrosis. Several epigenetic factors are implicated in the immune system; for example, HLA-DR7,¹¹ an intronic AAT-repeat in the neuronal nitric oxide synthase gene,¹² and polymorphisms in α_1 -antitrypsin^{13,14} and mannose binding lectin¹⁵ genes have been reported to affect rate of *Pseudomonas aeruginosa* airway infection in patients with cystic fibrosis.

CFTR is activated via cAMP through β_2 adrenoreceptor stimulation, and coding sequence polymorphisms in the gene for this protein might contribute to the disease state in cystic fibrosis.¹⁶ In mice with this disease, the occurrence of meconium ileus has been linked to a marker on chromosome 19q13.¹⁷ Modifying genes are likely to affect many different aspects of the cystic fibrosis phenotype, which therefore remains difficult to predict from CFTR mutation data alone.

Besides its function as a chloride channel, CFTR regulates other apical membrane conductance pathways.⁶ In airway epithelial cells of patients with cystic fibrosis, chloride impermeability caused by mutated CFTR, and increased sodium absorption¹⁸ caused by the epithelial sodium channel, raise the transepithelial potential difference (normal <30 mV; cystic fibrosis >35 mV). Whether activity of this sodium channel is inversely related to CFTR activity, or whether it is activated by CFTR, is unclear.^{19,20} CFTR is thought to regulate the outwardly rectifying chloride channel by facilitating cellular release of ATP. Once released, ATP might stimulate the channel through a purinergic receptor.²¹ Data suggest that CFTR also transports HCO₃⁻ or regulates its transport through epithelial cell membranes.²²

Pathophysiology

Pulmonary infection and inflammation

Cystic fibrosis leads to pathological changes in organs that express CFTR, including secretory cells, sinuses, lungs, pancreas, liver, and reproductive tract. The most striking changes are seen in airways, in which the basic genetic defect causes chronic pulmonary infections with surprisingly few bacterial pathogens. Overall, *P aeruginosa* is the most common isolate, followed by *Staphylococcus aureus*, *Haemophilus influenzae*, and *Stenotrophomonas maltophilia*.²³ Several hypotheses link mutations in CFTR to development of these infections, and we discuss these below.

The inflammation-first hypothesis proposes that inflammation is present in airways of a patient with cystic fibrosis in the first months of life before infection,²⁴ a finding that is lent support by work in germ-free raised mice with the disease²⁵ and severe combined

Search strategy

Data for this seminar were selected by searches of Medline with the keyword "cystic fibrosis and CFTR" from June, 2002, to 1980, which yielded 16 828 references. Citations were used on the basis of relevance to the topic from articles published in English. Furthermore, key studies related to cystic fibrosis published at an earlier date and known to the authors were also included. Special focus was put on work published since the last review on cystic fibrosis in *The Lancet* in 1998. The description of treatment approaches is based on evidence provided by randomised controlled trials and on Cochrane reviews of therapeutic strategies.

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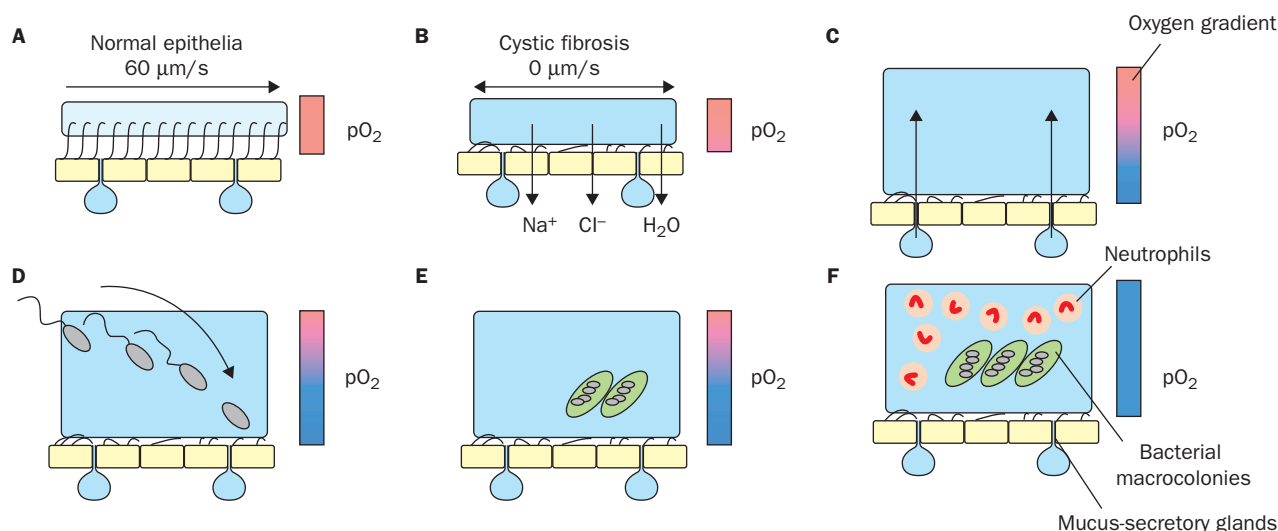


Figure 1: Pathogenic idea of cystic fibrosis lung disease

Blue circles=mucus layer; yellow squares=airway epithelial cells. For oxygen gradient: red=no gradient; blue=steep, hypoxic gradient. Because of blocked chloride secretion, excessive sodium absorption and water absorption, normal mucociliary clearance (A) is defective in cystic fibrosis (B). Mucus secretion leads to plug formation (C). Steep hypoxic gradients (blue bar) are sensed by penetrating bacteria (D) leading to increased alginate (E) and macrocolony formation (F). Neutrophil functions are impaired by anoxic conditions and macrocolonies (F). Adapted from reference 38 with permission of the *Journal of Clinical Investigation*.

immunodeficient mice grafted with cystic fibrosis fetal lung tissue.²⁶ However, findings of other investigators²⁷ do not accord with this hypothesis, and emphasise that inflammation follows infection. Other evidence shows that cystic fibrosis bronchoalveolar lavage fluids contain—and bronchial epithelial cells produce²⁸—low concentrations of the anti-inflammatory cytokine interleukin 10. Deficiency of this interleukin leads to severe lung inflammation after challenge with *P aeruginosa* in mice.²⁹

The cell-receptor hypothesis suggests that cystic fibrosis cell organelles are more acidic³⁰ or alkaline³¹ than organelles from normal cells, and that altered pH leads to reduced sialylation of glycoconjugates on cystic fibrosis epithelial cell membranes. Increasing numbers of asialoGM1 molecules—a receptor for many bacterial respiratory pathogens—have been reported on cystic fibrosis epithelial cells, resulting in increased binding of *P aeruginosa*^{30,31} and *S aureus*³¹ on these cells. CFTR has been characterised as a receptor for *P aeruginosa*, which—displaying normal function—internalises and kills the pathogen.³² By contrast, F508del CFTR cannot bind this pathogen, leaving bacteria free to multiply in the airway lumen of patients with cystic fibrosis.³²

The salt-defensin hypothesis is based on the assumption that cystic fibrosis airway epithelial cells have closely similar properties to sweat glands—ie, raised luminal salt concentration.^{33,34} Since defensins are inactivated by a salt concentration of greater than 50 mmol/L, bacteria can multiply on respiratory epithelial cell surfaces of patients with cystic fibrosis, leading to infections.³³ This hypothesis is lent support by work in human bronchial xenografts,³⁵ but results of an in-vivo study did not replicate this finding.³⁶

These hypotheses do not account for why *S aureus* and *P aeruginosa* show a mucoid phenotype in cystic fibrosis. The inflammation-first and salt-defensin hypotheses do not account for the appearance of these selected pathogens, whereas the cell-receptor hypothesis does not explain infections with *S aureus* and *H influenzae*.

The isotonic fluid depletion/anoxic mucus hypothesis proposes isotonic salt concentrations as a result of abnormal sodium absorption from the airway lumen,

coupled with failure of CFTR to secrete chloride,³⁷ leading to a water/volume depleted periciliary liquid (figure 1). Water loss increases mucus viscosity and impairs mucociliary clearance and cough clearance. Bacteria invading the cystic fibrosis lung are trapped in this viscous mucus layer on top of respiratory epithelial cells, in which they encounter microaerophilic or anaerobic growth conditions attributable to abnormal oxygen consumption of the cystic fibrosis cell.³⁸ These growth conditions trigger a switch of *S aureus* and *P aeruginosa* from non-mucoid to mucoid cell-types,³⁸ the main phenotype in cystic fibrosis lungs. However, other stimuli—including reactive oxygen species such as hydrogen peroxide—also trigger this mucoid switch of *P aeruginosa*.³⁹

Although these hypotheses can be disputed, an exaggerated, sustained, and extended inflammatory response to bacterial and viral pathogens—characterised by neutrophil dominated airway inflammation—is an accepted feature of lung disease in cystic fibrosis. Inflammation is present even in clinically stable patients with some lung disease and in young infants diagnosed by neonatal screening.^{24,27,40} Persistent endobronchial inflammation is thought to be deleterious for the course of lung disease. Quantification of airway inflammation is necessary to monitor its evolution over time and the effect of anti-inflammatory treatment. This monitoring remains a difficult task, since reliable non-invasive markers of airway inflammation are not available.

Pancreatic insufficiency and diabetes

Exocrine pancreatic insufficiency is present in about 90% of patients with cystic fibrosis. Pancreatic disease is thought to result from a reduced volume of pancreatic secretion with low concentrations of HCO_3^- .⁴¹ Without sufficient fluid and HCO_3^- , digestive proenzymes are retained in pancreatic ducts and prematurely activated, ultimately leading to tissue destruction and fibrosis. The resulting malabsorption contributes to the failure to meet raised energy demands caused by the hypermetabolic state associated with endobronchial infection. An inverse correlation exists between energy demands and lung

function.⁴² Since lung infections can lead to reduced appetite and vomiting, malnutrition is further enhanced. These factors might exacerbate lung infection, leading to a vicious cycle of malnutrition and infection.

Langerhans cells are initially spared from pancreatic fibrosis, and diabetes mellitus is rare in the first decade of the patient's life; prevalence of this disease rises constantly with age.⁴³ Diabetes in patients with cystic fibrosis shares features of the type 1 and 2 disorder, and a combination of reduced and delayed insulin secretion with insulin resistance is present in most patients.^{43,44}

Biliary disorders

CFTR is expressed in cells of the biliary tract, and at least a third of patients have abnormal results of liver function tests. Fatty infiltration is reported in up to 70% of older patients; in fewer than 10% of these, this infiltration progresses to biliary cirrhosis. Histological changes include intraluminal concretions in the biliary tree, with duct dilatation. Bile-duct epithelium becomes hyperplastic and proliferates, with periductal inflammation and fibrosis. A small, poorly functioning gallbladder is present in up to 30% of patients with cystic fibrosis, and gallstones in up to 10%.⁴⁵ Faecal loss of bile acids is raised, with resultant reduction of the bile-salt pool, and biliary lipid becomes lithogenic.⁴⁵ Infants can present with cholestasis from bile that has abnormal concentrations of constituents and is sticky.

Fertility

98% of men with cystic fibrosis are infertile, with aspermia secondary to atretic or absent vasa deferentia and dilated or absent seminal vesicles.⁴⁵ Sexual potency and spermatogenesis are normal, and men with this disorder have become fathers with techniques such as microscopic epididymal sperm aspiration and intracytoplasmic sperm injection. Female reproductive function is normal, although cervical mucus can be dehydrated, which might impair fertility.⁴⁶

Diagnosis and screening

Diagnosis

Clinical signs for diagnosis of cystic fibrosis are listed in the panel. Additionally, a positive family history or positive finding at newborn screening can be informative. Abnormal ion transport is shown by high concentrations in sweat of sodium and chloride and by a raised electrical

potential difference across the nasal epithelium. Both these features can be used for diagnosis.⁴⁷⁻⁴⁹ A concentration in sweat of chloride greater than 60 mmol/L on repeated analysis is diagnostic for cystic fibrosis, but about 5% of cases are false negative. Diagnosis can be confirmed by genotyping of the most common *CFTR* mutations;⁴⁷⁻⁴⁹ the range of mutations can vary from geographical region to region. *CFTR* genotyping is also recommended for patients with equivocal sweat test results. If this procedure is not diagnostic, a second test of CFTR function—such as nasal potential difference measurement or analysis of rectal mucosal biopsy specimens in an Ussing chamber—should be done.⁵⁰ Despite all these tests, a few patients remain in whom a definite diagnosis cannot be ascertained.⁵¹

Clinical tests that do not directly assess the *CFTR* defect can also aid diagnosis. 85–90% of patients with cystic fibrosis have pancreatic insufficiency, and a reduced faecal concentration of chymotrypsin or pancreas-specific elastase can confirm this disorder.^{52,53} Most patients with the disorder have total opacification of their paranasal sinuses and sinus radiography could be helpful.⁵⁴ Bacterial pathogens typical for cystic fibrosis (such as *P aeruginosa*) can be detected by analysis of sputum or throat-swab samples. Infertility due to congenital bilateral agenesis of the vas deferens is linked to *CFTR* mutations, but can also arise without other clinical signs of cystic fibrosis.⁵⁵ A diagnostic algorithm is presented in figure 2.

Screening

50% of all patients with cystic fibrosis in the USA are diagnosed by age 6 months, and 90% by age 8 years.²³ Neonatal screening programmes have been introduced in many countries, but whether early diagnosis will affect long-term outcome continues to cause controversy.⁵⁶ Modern screening programmes are based on a two-step approach: first, test for immune-reactive trypsin in dried blood spots; and second, confirm result by DNA analysis in positive cases.⁵⁷ Despite screening for cystic fibrosis being done in some areas of the world, only a few controlled studies have assessed its effect on long-term outcome of patients.⁵⁷ Results of a randomised screening programme in Wisconsin, USA, have shown that weight gain and early growth was better in patients diagnosed by neonatal screening than in those who were not diagnosed by this method.^{58,59} Since good nutrition is linked to a better prognosis,⁶⁰ these data favour introduction of population-wide neonatal screening. Benefit of early diagnosis might be counteracted by early exposure to cystic fibrosis pathogens in specialist centres if adequate hygienic measures are not implemented.⁶¹

Causative treatment

Ultimate curative treatment for cystic fibrosis is to restore CFTR function by transfection of cells with wild-type receptor.⁶² In-vivo gene therapy trials in patients with cystic fibrosis have been done with viral vectors and cationic lipids,^{63,64} however, long-term effects were not achieved. Repeat administration of adenovirus vectors reduces efficacy of transfection because of formation of specific antibodies,⁶⁵ whereas lipids might not specifically target CFTR-expressing cells. Therefore, although much progress has been made in gene therapy, it is presently not a treatment option for patients with cystic fibrosis.

Alternatively, intracellular production, trafficking, or activation of CFTR can be affected by treatment. Class 1 mutations lead to reduced production of CFTR mRNA, and gentamicin partly overcomes this problem.⁶⁶ In class 2 mutations, such as F508del, CFTR is trapped in the

Clinical signs of cystic fibrosis

Chronic airway disease

Chronic productive cough
Airway colonisation with pathogens (*S aureus*, mucoid *P aeruginosa*)
Persistent abnormalities on chest radiograph
Airway obstruction
Clubbing
Pansinusitis
Nasal polyps

Gastrointestinal disease

Meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
Pancreatic insufficiency, pancreatitis
Biliary cirrhosis
Failure to thrive, oedema with hypoproteinaemia, deficiency of fat-soluble vitamins

Pseudo-Bartter's syndrome (salt wasting with metabolic alkalosis)

Infertility due to obstructive azoospermia

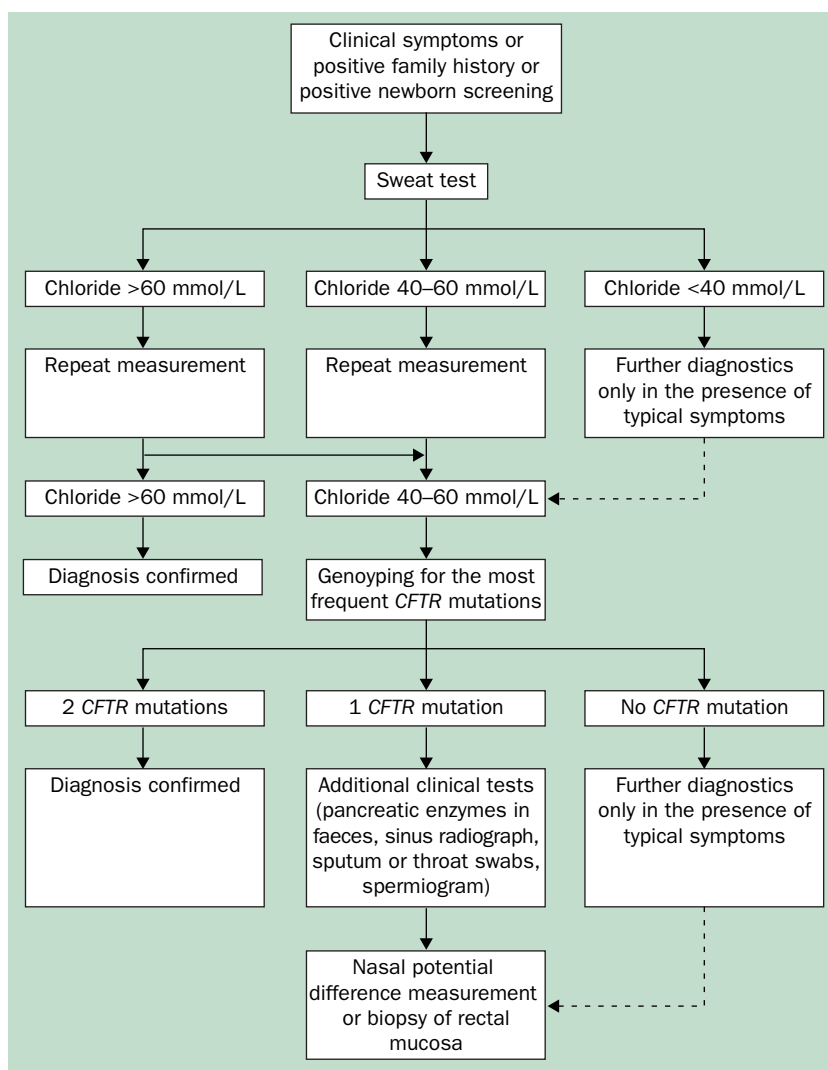


Figure 2: **Diagnostic algorithm**

endoplasmic reticulum and subsequently proteolytically degraded,^{67,68} but small amounts of F508del CFTR might reach the apical domain of respiratory epithelial cells in patients with cystic fibrosis.^{69,70} These findings suggest that F508del CFTR maturation can be modulated after passage through the endoplasmic reticulum. Compounds such as phenylbutyrate, CPX (8-cyclopentyl-1,3-dipropylxanthine) and genistein, which act as chaperones, have been tested in preliminary trials that have not included clinical endpoints.⁷¹⁻⁷³ High throughput screening technology is presently used in the search for further compounds.⁷⁴ Whether treatment with chaperones will result in sufficient concentrations of CFTR on the cell surface of epithelial cells is unclear. Furthermore, mutated CFTR that reaches the cell membrane might fail to function normally.⁷⁵ Additional targets of CFTR pharmacotherapy include activators of chloride secretion such as UTP (uridine triphosphate) or inhibitors of sodium absorption such as amiloride.^{76,77} Both drugs have a very short half-life, which restricts their efficacy, but newer compounds with an improved pharmacokinetic profile are being tested in preclinical trials.^{78,79}

Symptomatic treatment

Knowledge of the basic cystic fibrosis defect has led to many new ideas for causative treatment, but at present

treatment of the disorder is largely symptomatic. Many treatment ideas have been implemented into cystic fibrosis care, although sound scientific evidence is absent. For instance, chest physiotherapy is judged routine, but no studies have been done that prove its effect on the course of lung disease.

Infection

Prevention of bacterial lung infection is deemed a primary aim for cystic fibrosis treatment. Results of epidemiological studies suggest that transmission of *P aeruginosa* and other pathogens happens either by direct patient-to-patient contact or from various environmental bacterial reservoirs.⁸⁰ Improved hygienic measures and separation regimens have therefore been implemented in several specialist centres to limit cross-infection.⁸¹

Improved antibiotic treatment strategies against respiratory-tract infections is regarded as the main reason for the increased life expectancy of the patients with cystic fibrosis that has been achieved over past decades.⁸² Most patients are initially colonised with *S aureus* or *H influenzae*. Doctors generally agree to treat patients with pulmonary exacerbation with antistaphylococcal antibiotics for 2-4 weeks. Many cystic fibrosis centres try to eradicate bacteria from patients' airways with courses of oral antibiotics even in the absence of symptoms. In culture-positive patients, antistaphylococcal treatment for at least 2 weeks leads to an eradication rate of about 75%, and only a low proportion of patients

harbour *S aureus* for more than 6 months thereafter.⁸³ However, *S aureus* might persist intracellularly as small colony variants; these variants are sometimes missed on routine cultures, and can revert into normal strains after cessation of antibiotic treatment.⁸⁴

Prophylactic antistaphylococcal therapy with flucloxacillin initiated from time of diagnosis has been assessed in a controlled study.⁸⁵ Treatment resulted in a lower rate of *S aureus* cultures, less cough, and a lower rate of admissions during the observation period than in those who were not treated. However, in a retrospective analysis,⁸⁶ continuous antistaphylococcal therapy was associated with a higher rate of *P aeruginosa* acquisition, especially in the first 6 years of life. Similarly, in a placebo controlled multicentre study⁸⁷ of prophylactic cefalexin therapy from time of diagnosis up to age 6 years, researchers did not show any benefit of cephalexin on pulmonary function; yet a higher incidence of *P aeruginosa* was noted in treated patients. *P aeruginosa* infection increases pulmonary inflammation and has a negative effect on lung function when this pathogen persists. Whether this raised risk of *P aeruginosa* colonisation is specific for cephalosporins or applies to all anti-staphylococcal agents is unclear. Presently, insufficient evidence exists about whether the benefits of prophylactic antistaphylococcal therapy outweigh its risks.⁸⁸

Although the rate of *S aureus* infection in patients with cystic fibrosis falls with age, that of *P aeruginosa* increases, rendering this microorganism the major pathogen in this disorder.²³ After an initial transient colonisation period with non-mucoid strains, untreated patients generally become chronically infected with alginate-coated mucoid strains of *P aeruginosa*. Even with intensive antibiotic regimens, mucoid *P aeruginosa* cannot be eradicated, probably because of poor penetration of antibiotics into anaerobic sputum plugs³⁸ and rapid development of mutator strains, which show enhanced resistance to antimicrobial drugs.^{1,89}

European consensus on antibiotic therapy against *P aeruginosa* has been obtained.⁹⁰ Aggressive approaches, applying repeated courses of high-dose antibiotics, are warranted to avoid permanent pulmonary damage. Such a regimen has the risk that resistance towards a specific drug rises rapidly. Emergence of resistant microorganisms has been shown to be transient, reverting to susceptible over time when the selective pressure of the antibiotics is removed—an occurrence called adaptive resistance.⁹¹ Frequent changing from one antipseudomonal antibiotic to another might be an option to prevent *P aeruginosa* becoming resistant to antibiotics.

Although a European panel of experts recommended administration of regular intravenous antibiotics every 3 months—irrespective of respiratory symptoms—in chronically infected patients with cystic fibrosis, by contrast with treatment only in the presence of a pulmonary exacerbation,⁹⁰ no controlled trials with sufficient power have been done to compare this approach of maintenance therapy with that of therapy on demand.⁹² Regular intravenous treatment has been postulated to result in better clinical status and life expectancy of patients with cystic fibrosis,⁹³ but results of a randomised controlled trial did not show an advantage of this policy over symptomatic treatment.⁹⁴

To avoid adverse effects and to obtain high airway concentrations, the inhalation route has been used in the past two decades for antibiotic treatment in patients with cystic fibrosis. Both tobramycin (80 mg twice a day) and colistin (2×1 million IU) had positive effects on the clinical course of patients with chronic *P aeruginosa* infection.^{95,96} Additionally, a phenol-free preparation of tobramycin, given in a dose of 300 mg twice a day in 4-week intervals improved lung function and reduced sputum density of *P aeruginosa* in a placebo-controlled study.⁹⁷ How this form of treatment compares with conventional doses and preparation of tobramycin is unclear.⁹⁸

Macrolide antibiotics have received attention in patients positive for *P aeruginosa* because of their remarkable effect in those with diffuse panbronchiolitis.⁹⁹ Results of studies have confirmed initial reports of a benefit in patients with cystic fibrosis with moderate-to-severe lung disease.^{100–103}

A major improvement in the strategy to fight pulmonary *P aeruginosa* infection in patients with cystic fibrosis is early antibiotic treatment. In the early phase of *P aeruginosa* colonisation, antibiotics can avoid the shift to chronic mucoid infection. The combination of inhaled colistin with oral ciprofloxacin, or inhaled colistin or inhaled tobramycin alone, has been used to treat early *P aeruginosa* colonisation.^{104–106} Long-term follow-up of patients treated with inhaled tobramycin at a dose of 80 mg twice a day for 1 year after initial colonisation with *P aeruginosa* showed that it not only postponed chronic infection but also led to eradication of the bacteria in 14 of 15 treated patients.¹⁰⁷ Although the optimum treatment regimen for early *P aeruginosa* colonisation—ie,

length of treatment, drug concentrations, and combinations—has yet to be established, this regimen will most probably reduce rate of chronic airway infection with this pathogen in patients with cystic fibrosis.

Inflammation

As outlined above, cystic fibrosis is characterised by intense, neutrophil-dominated airway inflammation. This inflammation can be treated with drugs that have pleiotropic effects on neutrophils, that block specifically proinflammatory cytokines, or that target specific components of neutrophils. Early trials of anti-inflammatory treatment have been done with corticosteroids. Oral prednisone (2 mg/kg bodyweight every other day) improved lung function and reduced frequency of pulmonary exacerbations in a pilot study.¹⁰⁸ A large multicentre study in the USA, comparing placebo with prednisone in doses of 1 and 2 mg/kg bodyweight every other day, was reported to reduce the decline of lung function for the first 2 years only in patients positive for *P aeruginosa*, but serious side-effects such as glucose intolerance and cataracts were noted in prednisone-treated patients.¹⁰⁹ Furthermore, growth retardation was seen that persisted into adulthood.¹¹⁰ Therefore, the risk/benefit ratio does not favour long-term prednisone treatment in patients with cystic fibrosis.¹¹¹

Treatment with inhaled steroids should reduce adverse effects, but results of a controlled study show a beneficial effect, mainly on airway hyper-reactivity, whereas clear benefits for pulmonary function were not shown.¹¹² As a result, non-steroidal anti-inflammatory drugs such as ibuprofen have been proposed for treatment. High-dose ibuprofen slowed lung function decline in patients with cystic fibrosis, but benefit was most evident in a subgroup of patients aged 5–13 years.¹¹³ The major disadvantage of ibuprofen relates to its narrow treatment window, which implies that concentrations of the drug in serum have to be carefully assessed in all patients. Low concentrations might increase neutrophil influx in the lung, and high concentrations are associated with a raised risk of side-effects such as gastrointestinal bleeding. Several other anti-inflammatory drugs—eg, recombinant interleukin 10, anti interleukin 8, or leukotriene B₄ receptor antagonists—have been developed, but their effectiveness in treatment of cystic fibrosis is unclear.

As a result of neutrophil degradation in cystic fibrosis airways, high concentrations of enzymatically active serine proteases are present in chronically infected patients with this disorder, which are implicated in destruction of airway tissues.¹¹⁴ Therefore, a strategy of increasing antiprotease concentrations in the lung by supplementation with suitable inhibitors has been proposed. Recombinant human secretory leucocyte proteinase inhibitor aerosol treatment in patients with cystic fibrosis caused a striking reduction in interleukin 8 concentrations in the epithelial lining fluid.¹¹⁵ However, the pharmacokinetics of this treatment repeatedly administered by aerosol to healthy individuals or patients with cystic fibrosis showed that it does not accumulate on the respiratory epithelial surface.¹¹⁶ A trial with α_1 -proteinase inhibitor aerosol treatment in a few patients with cystic fibrosis for several weeks gave promising results,¹¹⁷ and *P aeruginosa* colony counts were reduced in rats with chronic *P aeruginosa* lung infection.¹¹⁸ Thus, inhibition of neutrophil serine proteases might restore neutrophil function and reduce mucus hypersecretion. Large studies are needed to substantiate the noted effects. Viscid airway secretions are a characteristic of cystic fibrosis lung disease. Classic

mucolytics such as *N*-acetylcysteine have little effect on lung disease in patients with this disorder.¹¹⁹ By contrast, recombinant human DNase has been reported to reduce sputum viscosity, improve pulmonary function, and reduce number of pulmonary exacerbations in patients with moderate¹²⁰ and mild¹²¹ lung disease. Also, short-term application of hypertonic saline improves airway clearance and lung function, though to a lesser extent than recombinant human DNase.^{122,123} The effect of long-term treatment with this drug or hypertonic saline on course of cystic fibrosis lung disease is as yet unknown.^{122,124}

Lung transplantation

Double lung or heart-lung transplantation is a treatment option for patients with cystic fibrosis and end-stage lung disease. Overall survival of lung-transplant patients is poorer than for other organ transplantation, with 3-year survival of about 60% in patients with cystic fibrosis (<http://www.ishlt.org>).¹²⁵ Generally, survival is better for adults than for children,¹²⁶ but some centres have reported a survival benefit in children.¹²⁷ Graft survival is worse for patients infected with *Burkholderia cepacia* genomovar III.¹²⁸ Although to find the right timepoint to put a patient on a transplant list remains difficult, most centres judge a forced expiratory volume in 1 s below 30% in a patient receiving maximum medical treatment to be a good indicator for assessment for lung transplantation.¹²⁹ Living-related organ transplantation, and even unrelated-donor lung transplantation, have been done in some centres;¹³⁰ these procedures raise several ethical issues that are beyond the scope of this seminar.

Pancreatic insufficiency, nutrition, and liver disease

Patients with cystic fibrosis and poor nutritional status are more prone to chest infections than those who have good nutritional status, and those with normal fat absorption have a better pulmonary prognosis than those who do not.^{59,131} Poor nutritional status has been linked to worse prognosis of patients with cystic fibrosis,¹³² a finding that has prompted an aggressive approach to maintenance of normal weight in patients with this disorder. Introduction of acid-resistant microspheric pancreatic enzyme preparations in the 1970s has greatly improved, but not returned to normal, weight of patients with cystic fibrosis, and European consensus was reached on optimum nutrition.¹³³ Unfortunately, oral caloric supplements and enteral feeding by nasogastric tube or gastrostomy tube have been introduced clinically before doing adequate scientific studies.^{134,135}

Ursodeoxycholic acid has been shown to return raised liver enzyme concentrations to normal, but its long-term effect on evolution of liver disease remains largely unproven.¹³⁶ Liver disease is a life-limiting factor in only a few patients, but liver transplantation has been successfully undertaken in individuals with advanced liver and limited pulmonary disease.¹³⁷

Prognosis

Data from the US registry show that median age at death in patients with cystic fibrosis has risen from 8.4 years in 1969, to 14.3 years in 1998, and the median age of survival rose from 14 years in 1969 to 32 years in 2000.²³ Similar improvements have taken place in other countries, but significant differences in survival persist.¹³⁸ These differences might be affected by treatment strategies, access to specialised centres, and socioeconomic status, which have all been postulated to affect long-term outcome.^{139,140}

Future directions and developments

To further improve life expectancy in patients with cystic fibrosis, a better understanding of the pathophysiology leading to lung disease is necessary, which includes further research on mechanisms of airway-surface liquid-volume depletion, mucus secretion, and mucociliary clearance. A thorough description of in-vivo gene expression and survival strategies of bacterial pathogens relevant for cystic fibrosis is needed to explore new antimicrobial drug targets. Improved anti-inflammatory and antimicrobial treatment regimens, and prevention strategies based on vaccination, could decrease neutrophil-dominated inflammation and prevalence of *P aeruginosa* infections, thus preserving lung function. Whether such a trend will subsequently lead to a shift to other pathogens in the cystic fibrosis airways is not known. Furthermore, because of high-throughput screening technologies, an increasing number of drugs positively affecting ion-channel functions are being developed. This development could lead to a change in treatment strategy, from a symptomatic approach to pharmacotherapy targeting the basic *CFTR* defect.

Conflict of interest statement

None declared.

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Uses of error

What you want to see

Paul Georg Lankisch

In 35 years of clinical practice, almost half of it in a leading position, I have made my fair share of mistakes, but some show the same pattern. The first incident was a 22-year-old man, transferred to us from a smaller hospital, who had severe acute necrotising pancreatitis. With the waiting-room full of other patients I hastened to ask symptom-related questions, quickly examined the abdomen, and sent him to the ward. There, it was assumed that I had fully examined the patient and had taken a case history and therefore the physical examination was not completed. Only by chance, a nurse asked him to provide a faecal specimen to test for occult blood. This was not a common procedure in younger patients at that time. All tests were positive. Family history and a rectal examination revealed familial adenomatous polyposis and several polyps in the rectum. A colectomy showed many premalignancies.

The second incident was a 35-year-old woman with severe pneumonia. She did not improve. Every morning I examined her lungs and adjusted the antibiotic treatment several times. When I was off duty, my senior registrar did not stop at the lungs but auscultated the heart to find aortic insufficiency due to endocarditis which was not present at my first examination. Despite an immediate operation she died.

The third incident was sad, too. A 65-year-old man was sent for a laparoscopic cholecystectomy after acute pancreatitis. This was assumed to be of biliary origin as gallstones were found on ultrasonography. A preoperative

ERCP revealed a partial obstruction of the pancreatic duct between the head and the body of the pancreas. Ultrasound, endoscopic ultrasound, contrast-enhanced computed tomogram, and even pancreatoscopy failed to show a tumour. I had never heard of the main duct being affected after acute pancreatitis. Nevertheless, in the presence of so many negative imaging results I believed that this was perhaps a first case and arranged a dilatation of the stenosis. 11 months later, the patient complained of severe abdominal pain. A tumour was now seen on the recently available magnetic resonance tomography. Laparotomy showed an advanced inoperable adenocarcinoma of the pancreas. The patient died a few months later.

Three times I had seen what I wanted to see. Only chance prevented a fatal outcome in the first case, where a few more questions would have changed everything. A more thorough examination of the patient when treatment seemed to fail would have led to an earlier diagnosis in the second case. If I had relied more on my own judgment the third patient would have been operated on much earlier for a tumour-induced acute pancreatitis and would have stood a better chance.

Time does not allow you a replay and you are very rarely granted a second chance. So, try not to see what you want to see and what seems to be obvious, look beyond. Insist on a full case-history and examination and restart again if the patient does not respond as would be expected. Few know better than I how difficult this is.

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