CONTINUING MEDICAL EDUCATION

Cystic Fibrosis

Diagnosis and Treatment

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SUMMARY

Background: Universal screening of newborn babies for cystic fibrosis was launched in Germany on 1 September 2016. Here we present up-to-date information on the diagnosis, treatment, and prognosis of this disease.

Methods: This article is based on relevant publications retrieved by a selective search in PubMed, along with guidelines from Germany and abroad and systematic reviews.

Results: Cystic fibrosis is caused by a gene mutation leading to dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. It affects multiple organ systems—the lungs, pancreas, upper airways, liver, intestine, and reproductive organs—to varying degrees. Its incidence among newborn babies in Germany is between 1 in 3300 and 1 in 4800. Its diagnosis requires both clinical evidence (positive newborn screening, sibling[s] with cystic fibrosis, clinical signs) and the demonstration of CFTR dysfunction by an elevated chloride concentration in sweat, and/or two disease-causing mutations, and/or abnormal electrophysiological findings (nasal potential difference measurement, intestinal short-circuit current measurement). Patients should be cared for by specialized cystic fibrosis centers in close cooperation with their primary care physicians. The median life span of patients with this disease has risen steadily to the current value of 40 years. Aside from symptomatic treatment, the first mutation-specific treatments have recently become available.

Conclusion: Early diagnosis and optimized treatment prolong the lives of persons with cystic fibrosis and improve their quality of life. Causally directed treatment for all patients and their effects on the course of disease are now central issues for further research.

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Cystic fibrosis (mucoviscidosis) is the most common life-shortening multisystem disease with an autosomal recessive inheritance pattern in Germany today, affecting 1 in 3300 to 1 in 4800 neonates (1, 2). It is caused by dysfunction of the chloride channels of exocrine glands, specifically of the so-called cystic fibrosis transmembrane conductance regulator (CFTR) protein. It mainly involves the lungs and pancreas, but also the upper airways, liver, intestine, and reproductive organs (*Table*). Improved diagnosis and symptomatic treatment have improved the health and survival prospects of persons with this disease, from a life span of only a few months in the 1950s (e1) to a median of 40 years today (3). Of the estimated 6000–7000 patients in Germany at present, 57 % are over age 18 (4). The approval of causally directed, mutation-specific treatments and the initiation of universal neonatal screening for cystic fibrosis in Germany on 1 September 2016 (5) are the occasion for this review of its current diagnosis and treatment.

Method

This review is based on pertinent publications retrieved by a selective search in PubMed, as well as on the guidelines of the the Association of the Scientific Medical Societies in Germany (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.*, AWMF), the European Cystic Fibrosis Society, and the Cystic Fibrosis Foundation (USA).

Learning goals

This article should enable the reader to:

- know the clinical signs of cystic fibrosis, the procedure for neonatal screening, and the confirmatory tests to be ordered in case of a positive screening test;
- gain an overview of the current state of symptomatic and causally directed treatment;
- recognize complications and accompanying conditions, and assess the patient's prognosis.

Epidemiology

Cystic fibrosis is a genetic disease of autosomal recessive inheritance affecting 1 in 3300 to 1 in 4800 neonates in Germany.

Clinical features of cystic fibrosis

Cystic fibrosis is caused by dysfunction of the CFTR protein, a chloride channel of exocrine glands. The defect leads to diminished chloride secretion and, in turn, to increased sodium absorption through epithelial sodium channels and removal of water from secretions, which are therefore abnormally viscous (6). The consequences include obstruction, inflammation, infection (in the lungs and upper airways), and ensuing tissue reorganization and loss of function. The severity of the disease in the individual case partly depends on variable organ sensitivity and on the genetically determined residual function of the CFTR protein. 99% of the affected male patients are infertile because of obstructive azoospermia, and 87% of patients have exocrine pancreatic insufficiency. Disease severity—particularly the degree of pulmonary involvement, which is a crucial determinant of morbidity and mortality—also depends on other disease-modifying genes (7) and on the patient's socioeconomic setting (8).

Exocrine pancreatic insufficiency (PI) is a characteristic type of organ involvement in cystic fibrosis. It is manifested by voluminous, fatty, shiny, malodorous, pulpy stools, abdominal symptoms, dystrophy, and deficiencies of fat-soluble vitamins (e.g., hemolytic anemia due to vitamin E deficiency) and trace elements (e.g., zinc dermatosis). The diagnosis can be established by a low fecal elastase measurement. Patients with primary pancreatic insufficiency are at elevated risk of chronic and/or recurrent pancreatitis (e2).

The course of chronic disease of the lungs and paranasal sinuses varies among patients with cystic fibrosis and can be hard to distinguish from frequent recurrent bouts of bronchitis and/or pneumonia, especially in preschool children. Children suffering from cough, sputum production, or wheezing of more than three months' duration, persistently abnormal radiological findings, persistently positive bacterial cultures of respiratory secretions, or clubbing of the fingers should undergo diagnostic testing for cystic fibrosis even if their neonatal screening test was negative. The same holds for children with bilateral chronic rhinosinusitis with frequent exacerbations (with or without nasal polyps).

Meconium ileus leads to a diagnosis of cystic fibrosis in 20% of all affected children, sometimes prenatally. All neonates with meconium ileus, intestinal atresia, or volvulus should be tested for cystic fibrosis. Rarer clinical manifestations of cystic fibrosis include:

TABLE

Organ involvement

Organ	Type of involvement	Frequency
Lung	chronic pneumonia, fibrosis	99%
Nose	chronic rhinosinusitis	61% (e12)
	polyposis of the nose and sinuses	46% (e12)
Liver	steatosis	25–60% (29)
	cirrhosis	10% (29)
	cholecystolithiasis	15% (28)
Pancreas	exocrine pancreatic insufficiency	87% (4)
	diabetes mellitus	32% (4)
	pancreatitis	2% (e2)
Intestine	meconium ileus	20% (e13)
	distal intestinal obstruction syndrome	6% (4)
Reproductive tract	obstructive azoospermia	97% (e14)

- hypochloremic alkalosis without vomiting in children (salt-wasting syndrome);
- chronic liver disease, especially focal biliary or multilobular cirrhosis;
- prolonged neonatal icterus;
- obstructive azoospermia.

As cystic fibrosis is inherited in an autosomal recessive pattern, the siblings of affected children have a 25% chance of being affected (e3) and should be tested for the disease whether or not they have symptoms.

Neonatal screening

In 2015, only 55% of children with cystic fibrosis in Germany received the diagnosis during the first year of life (4). 40% of newly diagnosed patients had either pulmonary or gastrointestinal manifestations at the time of diagnosis, and 20% had both (e4). Most patients by this time already had prognostically unfavorable complications, such as underweight and lung damage, which could have been prevented by earlier diagnosis and treatment. Neonatal screening for cystic fibrosis has been performed for years in many countries and has had beneficial effects on the affected patients' physical development, pulmonary function, and survival (9, 10). Universal neonatal screening for cystic fibrosis was initiated in Germany on 1 September 2016

Pathogenesis

Cystic fibrosis is caused by dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel of exocrine glands.

Clinical signs

These include failure to thrive and chronic cough, as well as meconium ileus in the neonate, chronic bilateral rhinosinusitis in childhood, biliary hepatic cirrhosis, and obstructive azoospermia.

Neonatal

screening, modified from (5)

*The cutoff value of PAP depends on the test kit used and corresponds to the 87.5th percentile in the normal population.

FIGURE 1

(5). Perinatal pancreatic damage is assessed by the measurement of immune-reactive trypsin (IRT; sensitivity 85.7%, specificity 99.8% [e5]) and pancreatitis-associated protein (PAP) in the blood. The combination of these tests with a genetic test for the 31 most common CFTR mutations in Germany yields a sensitive and specific screening test based on a single blood sample (Figure 1). Five of every 5000 screening tests yield findings requiring further evaluation, and one screening test in 5000 ultimately leads to a diagnosis of cystic fibrosis. Parental informed consent for a screening test can only be obtained by a physician, because of the genetic diagnosis contained in the test; if a child is born with the assistance of a midwife only, screening for cystic fibrosis must be carried out by a physician within 28 days of birth. In order to preserve the parents' right not to know, not all samples are studied genetically, and the physician ordering the test is not given the individual results of the IRT, PAP, and genetic components of the test, but only the qualitative overall result (positive or negative screening test). The physician informs the parents of the results and of the

confirmatory studies that must be performed, in case of a positive test, in a specialized cystic fibrosis center. The parents must contact the center themselves. Simultaneous information to the ordering physician and to a specialized center near the patient's residence, direct information to the parents with an invitation to them to come to the center, and compulsory tracking by the screening laboratories are components of an approach that has been found to be successful in Switzerland and elsewhere (11). These measures were not, however, implemented in Germany, for a number of reasons including the absence of acute mortal danger, the need to maintain the confidentiality of medical data, and the right to choose one's physician freely. Instead, the chosen procedure puts the most sensitive information in the hands of the physician ordering the test (usually an obstetrician), makes the parents responsible for organizing appointments for confirmatory testing, and dispenses with compulsory tracking. An evaluation is planned to determine how effectively this procedure meets the goal of rapid and complete evaluation of all children who need it. It must be borne in mind that

Neonatal screening

Universal neonatal screening for cystic fibrosis was initiated in Germany on 1 September 2016 it consists of the measurement of immune-reactive trypsin and pancreatitis-associated protein along with a test for common CFTR mutations.

Prevalence

Of 5000 screening tests performed, 5 will be positive and further testing will confirm the diagnosis of cystic fibrosis in 1 patient.

babies with cystic fibrosis who have meconium ileus can have false-negative IRT values (12); therefore, babies with meconium ileus should be further tested for cystic fibrosis regardless of the screening results. A negative screening test makes cystic fibrosis unlikely, but does not rule it out, and further testing should be performed whenever the disease is suspected on clinical grounds. In London and the southeast of England, 7% (n = 16) of the children ultimately given the diagnosis of cystic fibrosis in the first 4 years after the introduction of screening had had a false-negative screening test (13).

Confirmatory testing

The diagnosis of cystic fibrosis requires at least one clinical feature of the disease, and/or a history of a sibling with the disease, and/or a positive neonatal screening test, as well as the demonstration of CFTR dysfunction (14) (*Box 1*). The latter can be established by a sweat test, by a molecular genetic test, or, in individual cases, by electrophysiological methods.

Chloride measurement in sweat is 96.5% sensitive and 99% specific and is the method of first choice. The informativeness of this test depends crucially on quality control in its performance and assessment, which is a requirement for certified cystic fibrosis centers. It can be carried out from the third day of life onward, and optimally from the 14th day of life onward, in children with a body weight of at least 3000 g and a gestational (postmenstrual) age of at least 36 weeks. The performance of two separate tests on a single day increases the rate of evaluable test results, especially in neonates. The demonstration of CFTR dysfunction requires high chloride values in sweat (≥ 60 mmol/L) in two independent measurements on the same day. Values below 29 mmol/L make cystic fibrosis unlikely; values between 30 and 59 mmol/L call for further diagnostic testing. The measurement of sweat conductivity is a widely performed test that is suitable only for screening, not for definitive diagnosis (14).

Molecular genetic tests constitute the second stage of confirmatory diagnostic testing. As there are more than 2000 known CFTR mutations on the long arm of chromosome 7, the informativeness of a test depends on the mutation spectrum that is investigated and on the patient's ethnic origin. 306 mutations have been characterized as causing disease (www.CFTR2.org). In many cases, this can be concluded from the type of the mutation itself. The most common mutation,

BOX 1

The diagnosis of cystic fibrosis (from [14])

- **CF is diagnosed when an individual has both:**
 - at least one clinical presentation of the disease, and evidence of CFTR dysfunction.
- **Clinical Presentation of CF includes:**
 - a positive neonatal screening test
 - a sibling carrying the diagnosis of cystic fibrosis
 - at least one clinical sign of cystic fibrosis
- **Evidence of CFTR dysfunction has to be demonstrated either by:**
 - an elevated chloride concentration in sweat (≥ 60 mmol/L) in at least two independent measurements, and/or
 - the demonstration of at least two cystic-fibrosis-causing CFTR mutations in trans, i.e., one mutation on each of the two chromosomes, and/or
 - the demonstration of a characteristic type of CFTR dysfunction with nasal potential difference measurement (NPD) or intestinal short-circuit current measurement (ICM).

CFTR, cystic fibrosis transmembrane conductance regulator

F508del, is present in 70% of German patients but in only 25% of patients of Turkish ethnic origin (1). The mutation spectrum investigated in the setting of neonatal screening in Germany (all mutations with frequency $\geq 0.1\%$) covers 95.5% of all CFTR mutations documented in the German cystic fibrosis registry in 2012 (5) and enables a definitive diagnosis by the demonstration of two disease-causing mutations in 90% of patients. A more time-consuming, complete investigation of the CFTR gene enables the detection of up to 99% of all mutations, so that two mutations can be found in 98% of all cystic fibrosis patients. Patients with a positive sweat test should undergo molecular genetic testing in order to confirm the diagnosis, enable genetic counseling of the family, and determine whether the option of mutation-specific treatment exists. Conversely, patients with a genetically confirmed diagnosis should undergo a sweat test to eliminate the possibility that the diagnosis resulted from an inadvertent switching of samples (14).

In individual cases, electrophysiological tests, such as intestinal short-circuit current measurement on biopsy samples of rectal mucosa and/or nasal potential

Confirmatory diagnostic testing

The test of first choice is the sweat test, followed by genetic analysis.

Pancreatic involvement

85% of patients with cystic fibrosis have exocrine pancreatic insufficiency. Further manifestations include "type 3" diabetes mellitus and recurrent bouts of pancreatitis.

BOX 2

Regular check-ups for patients with cystic fibrosis, after (25)

- **at least once every 3 months:**
 - height and weight
 - microbiological tests (throat and, if possible, sputum culture)
 - pulmonary function tests ($\geq$ age 6 at latest)
- **at least once per year:**
 - abdominal ultrasonography
 - oral glucose tolerance test ($\geq$ age 10)
 - inflammatory parameters
 - transaminases
 - serum fat-soluble vitamin levels
- **regularly (frequency debated):**
 - chest imaging (eg. chest x-ray, CT, MRT)

difference measurement, can be of use for patients whose diagnosis remains in doubt even after sweat testing and molecular genetic investigation (14).

The diagnosis and symptomatic treatment of cystic fibrosis

Further diagnostic evaluation after a positive screening test, definitive diagnosis, counseling, and treatment should be carried out in cooperation with the patient's primary care physician in a center possessing adequate experience in the diagnosis and treatment of cystic fibrosis, as recommended by current guidelines, with care provided by a multidisciplinary team consisting of physicians, physiotherapists, dieticians, psychologists, social workers, and nurses (15). From 2014 onward, qualified cystic fibrosis centers in Germany have been certified by the German Pediatric Pulmonology Society (*Gesellschaft für pädiatrische Pneumologie*) and the German Pulmonology Society (*Deutsche Gesellschaft für Pneumologie*), in collaboration with the German Cystic Fibrosis Association (*Mukoviszidose e. V.*; see www.muko.info/rd/zertifiziertezentren). The centers are required to participate in the German Cystic Fibrosis Registry and constitute a network of clinical trial

centers. All German cystic fibrosis centers face common challenges: inadequate financial support for the multidisciplinary team (16), a predicted rise in the number of adult patients (from 2590 in 2010 to a predicted 4380 in 2025) [17], and the transition from treatment by a pediatrician to treatment by an adult internist (18) (*Box 2*).

The main goals of treatment are age-appropriate physical and psychosocial development, especially with respect to pulmonary function and structure and body height and weight, and the avoidance of organ complications. According to the German cystic fibrosis registry for 2015, 74% of children, adolescents, and adults with cystic fibrosis are of normal weight; 77% of children and adolescents, and 28% of adults, have a normal one-second lung capacity (FEV_1) (4).

87% of patients with cystic fibrosis have exocrine pancreatic insufficiency, a problem that usually manifests itself in the first year of life (e6) and requires treatment with lifelong pancreatic enzyme supplementation, a high-calorie, high-fat diet with 110–220% of the recommended daily caloric intake for healthy persons which consists of 35–40% fat, and supplementation of fat-soluble vitamins and certain trace elements (19). The dose of gastric-acid-resistant pancreatic enzymes is calculated from the fat content of each meal (2000–4000 units of lipase per gram of fat) and optimized in relation to the patient's height and weight development. Serum levels of the fat-soluble vitamins A, D, and E, as well as the INR as an indication of vitamin K function, are checked at least once per year so that vitamin supplementation can be optimized. Age-adapted dietary counseling and education of persons in the patient's environment (e.g., kindergarten teachers) are just as important for age-appropriate development as regular clinical measurements (at least every three months). If the patient is underweight, the caloric intake must be increased by caloric enrichment of the diet, perhaps with the addition of a high-calorie dietary supplement—if necessary, in the form of special nocturnal dietary supplementation through a percutaneous endoscopic gastrostomy (PEG) (*Box 3*).

Chronic, progressive lung disease is by far the most common cause of death (in 77% of patients) (4). It is characterized by chronic endobronchial bacterial infection, infectious exacerbations, and pulmonary structural changes. The main goals of treatment are to improve mucociliary clearance, which is impaired by the underlying defect of the disease, by means of active

Lung disease

Impaired mucociliary clearance leads to chronic endobronchial bacterial infection, infectious exacerbations, and structural changes in the lungs (including emphysema/fibrosis).

Treatment goals

The main goals of treatment are to improve mucociliary clearance with by means of active respiratory therapy, exercise, and secretolytic therapies, and to prevent and suppress chronic bacterial infection with antibiotics.

respiratory therapy, exercise, and secretolytic therapies, and to prevent and suppress chronic bacterial infection with antibiotics. Respiratory therapy, under the direction of a physical therapist, includes techniques that the patient can carry out independently, including inhalation, effective coughing, mobilization of secretions, and use of the chest muscles. Sports and exercise reinforce respiratory therapy. The approved agents for secretolysis include osmotically active medications—hypertonic saline 6–7% for moist inhalation (reimbursable from age ≥ 6) and mannitol powder for dry inhalation (from age ≥ 18)—as well as rDNase for moist inhalation, which has mucolytic and anti-inflammatory effects (from age ≥ 6). Randomized, controlled trials (RCT) have shown that secretolytic therapy reduces infectious exacerbations (all agents) and improves FEV₁ (only mannitol and rDNase) (e7–e9). Problems that may limit the individual toleration of these important preventive treatments, particularly airway obstruction in osmotic therapy, necessitate an individual choice of treatment as well as physiotherapeutic support (20).

The most common bacteria causing endobronchial infection are *Staphylococcus aureus* (70% in childhood), *Haemophilus influenzae* (50% in childhood), and *Pseudomonas aeruginosa* (63% in adulthood) (3). The observed rise of multiresistant *Pseudomonas* strains, as well as other, rarer bacteria such as *Burkholderia*, *Achromobacter*, *Stenotrophomonas* and atypical mycobacteria, currently poses a therapeutic and hygienic challenge (21). Some centers recommend prophylactic antibiotic treatment against *Staphylococcus aureus*, though others prefer to give antibiotics sparingly to avoid selection of *Pseudomonas* (22). There is, however, a consensus that treatment is needed for exacerbations, which are characterized by increased coughing and expectoration, worsening pulmonary function, and sometimes changes that are apparent in laboratory tests or x-rays. These episodes are rarely associated with fever, are often virally triggered, and should be treated with antibiotics for 14–21 days, in accordance with the resistance pattern, after a throat culture has been taken. Pulmonary function tests show that pulmonary function fails to return to previous values in 25% of patients, even when treated with antibiotics (e10). Regular microbiological testing (throat culture / sputum if possible, at least once every 3 months) should be performed to assess bacterial colonization and enable early recognition of, among other

BOX 3

Symptomatic treatment

- **exocrine pancreatic insufficiency**
 - pancreatic enzymes
 - high-calorie, high-fat diet
 - fat-soluble vitamin supplementation
- **endocrine pancreatic insufficiency**
 - insulin therapy
- **liver disease**
 - ursodeoxycholic acid
- **lung disease**
 - respiratory therapy
 - (anti-obstructive therapy)
 - (anti-inflammatory therapy [corticosteroids])*
 - secretolytic therapy (hypertonic saline, mannitol, rDNase)
 - antibiotics
- **upper airways**
 - nasal rinses
 - nasal corticosteroids

*Anti-obstructive and anti-inflammatory therapy are not recommended as baseline treatment; rather, they are to be used as accompanying treatment, e.g., when inhalational antibiotics are given (anti-obstructive therapy) or when the patient also suffers from bronchial asthma (anti-inflammatory therapy).

things, an initial *Pseudomonas* infection. This makes eradication therapy possible, which, in the case of *Pseudomonas aeruginosa*, has contributed to the marked delay and reduction of chronic infection that has been seen over the past few decades. Oral/inhaled, exclusively inhaled, and intravenous treatment strategies are available for *Pseudomonas* eradication (23). Ciprofloxacin is approved for administration without any age limit to patients with cystic fibrosis (and other patients), in a liquid formulation as well. Suppression therapy is available for chronic endobronchial infection with the goal of reducing the infectious load and stabilizing the patient's clinical state. The approved agents for inhalation therapy to suppress *Pseudomonas aeruginosa* are tobramycin, colistin, aztreonam, and

Further manifestations

- liver involvement
- arthropathy
- osteoporosis
- distal intestinal obstruction syndrome

The basis of nutritional treatment

A high-calorie, high-fat diet and pancreatic enzyme supplementation are recommended depending on the degree of exocrine pancreatic insufficiency.

FIGURE 2

Complications of CF according to the American CF registry (e15) (with permission of the CF Foundation).
CF, cystic fibrosis

levofloxacin. Additional long-term oral anti-inflammatory treatment with azithromycin has been found effective (24). Regular treatment with intravenous antibiotics (e.g., every 3 months or every 14 days; two antibiotics in combination) are recommended by most centers depending on the extent of pulmonary disease, and by a few centers no matter what the extent of pulmonary disease (22). In addition to bacterial infections, allergic bronchopulmonary aspergillosis and fungal infections can affect the course of pulmonary function. There have not been any RCTs for antibiotic treatment strategies, with the exception of inhaled antibiotics (e11); they cannot be conducted because of the existence of generally accepted treatment standards.

Clinical examination at regular intervals, pulmonary function testing (body plethysmography every 3 months), and imaging studies (plain x-ray and computerized tomography or magnetic resonance imaging of the chest) are recommended for the assessment of chronically progressive lung disease and the optimization of its treatment (25). To detect early changes—in preschool children as well—gas-exchange methods can be used (lung clearance index). Of all pulmonary function parameters, the forced one-second capacity (FEV_1) has the greatest prognostic significance. The rate of loss of pulmonary function varies from patient to patient and is most pronounced in childhood and adolescence;

between the ages of 10 and 30, the average rate of loss is -2.3% of the predicted value ($FEV_1\%pred$) per year (26). The loss of pulmonary function is often not subjectively perceived until it drops below 40%. Lung transplantation should be discussed early with the patient if he or she is suffering from chronic respiratory insufficiency (partial or total) and the $FEV_1\%pred$ is less than 30% (27). The frequency of exacerbations, pneumothorax, hemoptysis, and rapid loss of pulmonary function are important indicators of the urgency of transplantation. 296 lungs were transplanted in Germany in 2015, 20% of which were given to patients with cystic fibrosis (28). Their 5-year survival rate after lung transplantation is 60%, the same as that of lung-transplant recipients with any underlying disease (27).

Cystic fibrosis is further complicated by the involvement of other organs. Liver involvement affects 32% of patients (4) and ranges from steatosis to hepatic fibrosis to secondary biliary hepatic cirrhosis (10%). Ursodeoxycholic acid is often given, despite scant evidence; liver transplantation is reserved for patients with severe portal hypertension and/or hepatic dysfunction (29). Liver involvement is usually diagnosed in childhood or adolescence by annual transaminase measurement and ultrasonographic screening. In contrast, the incidence of so-called type 3 diabetes mellitus, arthropathy, osteoporosis, and comorbid mental illnesses such as anxiety

Causally directed treatment

Mutation-specific treatment is available for approximately one-third of patients.

Prognosis

At present, the median life span of persons with cystic fibrosis is 40 years. Progressive lung disease is the most common cause of death.

and depression rises with age (*Figure 2*). Diabetes in cystic fibrosis is due to a combination of insulin resistance and diminished insulin secretion; it is recommended that all patients aged 10 years and older should have an annual oral glucose tolerance test for screening. The standard treatment is insulin therapy adapted to an unchanged high-calorie, high-fat diet (30). Osteopenia and osteoporosis are due to vitamin D deficiency and chronic inflammation, among other factors, and typically lead to rib and vertebral body fractures. A further complication is the distal intestinal obstruction syndrome (6%) (4), in which viscous intestinal secretions cause subileus. The emotional burden on the patient (whether a child, an adolescent, or an adult) and his or her parents may lead to anxiety and depression (prevalence 21% and 10%, respectively) (31), which can in turn impair treatment compliance and efficacy; these problems should be actively sought in an annual psychological screening (32). In the German-speaking countries, inpatient rehabilitation programs are an important component of treatment for the improvement of disease-related quality of life and self-management by the patients and their families. Patient and parent education on cystic fibrosis supplement these treatments.

Treating the cause of cystic fibrosis

The discovery of the CFTR gene in 1989 and the characterization of the function of CFTR raised the hope of a causally directed treatment. The first mutation-specific, orally administered systemic drug for cystic fibrosis was approved in 2012. This achievement was based on an understanding of the various functional effects of CFTR mutations, mass testing of substances in cell systems, and worldwide collaboration among cystic fibrosis centers (patient registries, trial networks). The active substance ivacaftor interacts with the CFTR protein and potentiates its effect. The drug has been shown in randomized and controlled trials to significantly improve pulmonary function (FEV_1 % pred absolute change: +10.6% [33]), body weight (+2.8 kg [33]), and the quality of life, and also to reduce infectious exacerbations (–55% [33]) and lower the chloride level in sweat (–47.9 mmol/L [33]; a direct indication of improved CFTR function), when it is given for 24 weeks to patients over age 6 who have at least one so-called gating mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R) (33, 34). For patients aged 2 to 6, a

body-weight-adapted granulate has been found to be safe and to lower the chloride level in sweat (35). Ivacaftor has been approved for patients aged 18 and above with the R117H mutation. Its main adverse effect is transient elevation of liver function parameters (these must be checked regularly). Cataract was seen in animal trials; therefore, ophthalmological examinations are recommended for children and adolescents before and during the use of the drug. Ivacaftor is a substrate of CYP3A4 and CYP3A5 and can therefore interact with other drugs. It can potentially be used by 3% of the cystic fibrosis patients in Germany.

F508del, the most common mutation causing cystic fibrosis (66% of patients in Germany), leads to faulty folding in the endoplasmic reticulum and, in turn, to premature degradation of the protein. The active substance lumacaftor stabilizes the protein, and ivacaftor potentiates its functional effect at the cell surface. A randomized and controlled trial of treatment with these two drugs over a period of 24 weeks revealed significant improvement of pulmonary function (absolute FEV_1 % pred: +2.8%) and of the body-mass index (+0.24 kg/m²) as well as a reduction of infectious exacerbations (–39%) in patients aged 12 and older who were homozygous for the F508del mutation (36). The improvement of pulmonary function, however, was much less than that seen with ivacaftor monotherapy for gating mutations. No significant improvement of the quality of life was found, and effects on CFTR function were not studied. The main adverse effects included a transient feeling of chest tightness (particularly in patients with a marked limitation of pulmonary function) and elevated liver function parameters (these must be checked regularly). With combination therapy, just as with ivacaftor monotherapy, ophthalmological examinations are recommended for children and adolescents. Lumacaftor strongly induces CYP3A and can therefore interact with many other drugs: for example, it weakens the effect of hormonal contraceptives. This treatment was approved in Germany in November 2015 for F508del homozygote patients aged 12 and above and can be used by 30% of the cystic fibrosis patients in Germany.

A phase 3 trial of ataluren for patients with stop mutations revealed no significant effect (37); the results of a follow-up study are pending. A recent 6-month phase 2b trial of mutation-independent inhalational gene therapy revealed no improvement from baseline, but a significant effect on pulmonary function compared

Rehabilitation

In the German-speaking countries, inpatient rehabilitation programs are an important component of treatment for the improvement of disease-related quality of life and self-management by the patients and their families.

Drug interactions

Lumacaftor strongly induces CYP3A and can therefore interact with many other drugs: for example, it weakens the effect of hormonal contraceptives.

with placebo (38); further trials are planned. Trials are also currently in progress for other mutations and other age groups ([39]; in Germany, [40]).

Mutation-specific treatments supplement but cannot replace symptomatic treatment. Their disease-modifying effect (on the loss of pulmonary function, mortality, and other endpoints) remains to be demonstrated in long-term epidemiologic studies. When these treatments (e.g., ivacaftor) are given, attention must be paid to the liver function parameters in particular. In the authors' view, early diagnosis, patient care in specialized multidisciplinary centers, and a combination of causally directed and symptomatic treatment will provide the foundation for further improvements in the lifetime perspectives of patients with cystic fibrosis.

Conflict of interest statement

PD Dr. Naehrlich has served as a paid consultant (Advisory Board, Steering Committee) for, and has received lecture honoraria from, the Vertex Pharmaceuticals (Germany) GmbH and Vertex Pharmaceuticals Inc. companies. He has received third-party funding for scientific research from Boehringer Ingelheim, Mpex Pharmaceutical, Aptalis, Gilead Sciences Inc., and Vertex Pharmaceuticals Inc.

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Mutation-specific treatments supplement but cannot replace symptomatic treatment. Their disease-modifying effect remains to be demonstrated in long-term epidemiologic studies.

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Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref3317

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the most appropriate answer.

Question 1

Which of the following symptoms is a clinical sign of cystic fibrosis?

- a) constipation
- b) arthralgia
- c) recurrent urinary tract infections
- d) dystrophy
- e) pustule-like vesicles

Question 2

After a midwife-assisted birth, when must a physician perform a cystic fibrosis screening test in Germany?

- a) up to the 28th day after birth
- b) up to the 42nd day after birth
- c) when the child is weaned
- d) with the U2 routine well-child examination
- e) with the U3 routine well-child examination

Question 3

What should all patients with cystic fibrosis, regardless of age, undergo at least once every 3 months?

- a) measurement of serum fat-soluble vitamin levels
- b) measurement of inflammatory parameters
- c) an oral glucose tolerance test
- d) abdominal ultrasonography
- e) microbiological testing

Question 4

What is the most important pathogen in the treatment of bacterial endobronchial infections in children with cystic fibrosis?

- a) *Stenotrophomonas*
- b) human respiratory syncytial virus
- c) *Pneumocystis jirovecii*
- d) *Pseudomonas aeruginosa*
- e) atypical mycobacteria

Question 5

What is often used in the symptomatic treatment of liver involvement in patients with cystic fibrosis, despite scant evidence?

- a) a high-calorie diet
- b) antibiotics
- c) fat-soluble vitamins
- d) ursodeoxycholic acid
- e) pancreatic enzymes

Question 6

What comorbid disease of patients with cystic fibrosis becomes increasingly common with age?

- a) mandibular necrosis
- b) glaucoma
- c) urticaria
- d) "type 3" diabetes mellitus
- e) hepatic cirrhosis

Question 7

What pathogen typically causes airway disease in patients with cystic fibrosis?

- a) *Streptococcus pneumoniae*
- b) *Neisseria meningitidis*
- c) *Pseudomonas aeruginosa*
- d) *Klebsiella pneumoniae*
- e) *Escherichia coli*

Question 8

Which lung function parameter has the greatest prognostic significance in the diagnosis of cystic fibrosis?

- a) forced vital capacity (FVC)
- b) one-second capacity (FEV₁)
- c) diffusion capacity (CO-Diff)
- d) airway resistance (R_{tot})
- e) Tiffeneau index (FEV₁/FVC)

Question 9

Which of the following is an integral component of standard symptomatic treatment for cystic fibrosis?

- a) acetylcysteine
- b) inhaled cortisone
- c) respiratory therapy
- d) vitamin C
- e) beta-blockers

Question 10

What, in particular, must be checked in patients receiving mutation-specific treatment for cystic fibrosis?

- a) the digestion
- b) the sleep-wake cycle
- c) the heart rhythm
- d) the blood pressure
- e) the liver values

Supplementary material to:

Cystic Fibrosis

Diagnosis and Treatment

by Susanne Naehrig, Cho-Ming Chao, and Lutz Naehrlich

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