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Comparison of surrogate parameters of prognosis (BMI, FEV1 and need of intravenous antibiotic therapy) between CF-patients with and without P. aeruginosa in Frankfurt and Moscow from 1990 to 2015

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List of abbreviations

ABPA	Allergic Bronchopulmonary Aspergillosis
ACFLD	Advanced Cystic Fibrosis Lung Disease
AP	Alcalic Phosphatase
ATS	American Thoracic Society
ATS/ERS	American Thoracic Society/ European Respiratory Society
BMI	Body Mass Index
BSR	Blood Sedimentation Rate
Ca2+	Calcium
cAMP	Cyclic Adenosine Monophosphate
CAUV	Congenital absence of the uterus and vagina
CBVAD	Congenital bilateral absence of the vas deferens
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane Regulator
CHE	Cholinesterase
Cl-	Chloride
cm	Centimeters
CRMS	CF related metabolic syndrome
DEXA	Dual Energy X-Ray Absorptiometry
e.g.	exempli gratia
etc.	et cetera
ECFS	European Cystic Fibrosis Society
ECFSPR	European Cystic Fibrosis Society Patient Registry
ERS	European Respiratory Society
F508del	Delta F508 mutation
FEV1	Forced Expiratory Volume in 1 second
Fig.	Figure
FMBA	Federal Medical-Biological Agency
FOR	Family Oriented Rehabilitation
FVC	Forced Vital Capacity

γ-GT	Gamma-glutamyltransferase
GLDH	Glutamate Dehydrogenase
HbA1c	Glycated hemoglobin, hemoglobin A1c
i.e.	Id est
i.v.	intravenous
IgE	Immunglobuline E
IgG	Immunglobuline G
INR	International Normalized Ratio
K+	Potassium
kb	Kilobase
kg	Kilograms
Mg2+	Magnesium
MHI	Mandatory health insurance
mL	Milliliter
mmol/L	Millimole per Liter
n	Number
Na+	Sodium
NaCl	Sodium Chloride
p	Significancy
P. aeruginosa / PA	Pseudomonas aeruginosa
PSA	Prostate-specific Antigen
PSC	Primary Sclerosing Cholangitis
PTT	Partial Thromboplastin Time
RAST	Radioallergosorbent Test
SD	Standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TIBC	Total Iron Binding Capacity
TTE	Transthoracic Echocardiography
vs.	Versus

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Keywords:

Cystic fibrosis, BMI, FEV1, intravenous antibiotic therapy, lung function, P. aeruginosa, surrogate parameters

1. Introduction

1.1. Overview and epidemiology

Cystic fibrosis (CF) is a rare genetic disease characterized by a loss of function of the cystic fibrosis transmembrane conductance regulator (CFTR) in different organs[1]. Inheritance of CF is autosomal recessive. It´s a rare disease and affects about 8000 known patients[2,3] in Germany in 2017. In Russia the ECFSPR (European Cystic Fibrosis Society Patient Registry) registered around 3200 patients[3] with an estimated coverage of 95%, which comes down to an estimated number of 3500 patients in the whole Russian Federation. In the last years, the lifetime prognosis of CF has increased all over the world due to earlier diagnosis and improved therapy including new medications. Newborn babies with CF in Germany have been calculated to have a lifetime prognosis reaching approximately 65 years[2]. According to the 2017 annual ECFSPR report more than 50% of German CF patients are older than 18 years (57.85% in 2017[3]). In Russia, more than 75% were at childhood age (76.13% under 18 years old in 2017[3]). CF patients' mean age in Germany was 22.4 years in 2017[3] and 12.4 years in Russia the same year[3]. Median age was 20.9 years in Germany while it was 9.9 years in Russia in 2017[3].

1.2. Etiology

The physiological basis of CF is a loss of function of the CFTR which is the result of a mutation in the CFTR gene located on a 250kb large region in the long arm of chromosome 7[1,4] . More than 2000 CFTR mutations have been reported according to John Hopkins University until June 2020[5,6]. Most of these are missense mutations amounting to more than 800, representing almost 40% of all known mutations. Frameshift mutations are also very widespread (more than 330 or approximately 16% of mutations[5]). The most common mutation in the world and in Germany in 2017 was the F508del (delta F508) mutations representing approximately 48 percent homozygotic and 35 percent heterozygotic mutations[3]. In comparison, among the Russian patients, the amount of F508del homozygotes in the CF popu-

lation was approximately 30 percent and F508del heterozygosity was found in 45 percent[3]. Patients who carry the F508del homozygotic mutation, although representing the largest group of CF patients, show a wide variety of the clinical disease phenotypes[7].

The CF gene is coding for an ABC (ATP-binding cassette) membrane protein which regulates the cAMP dependent chloride channel[4]. Five to six[8] different types of mutations have been described, where class I mutations induce a complete loss of function of the CFTR protein[9]. In contrast, class II mutations cause a synthesis defect[10], class III lead to a dysfunctional regulation[11], class IV are associated with a changed conductivity[12] of the channel, and class V mutations cause a lower stability[13] of the CFTR protein. In post endoplasmic reticulum compartments and the plasma membrane class VI mutations destabilize the channel[8].

In sequel of these mutations the produced CFTR channels are partially or completely inoperative or have a loss of function. Normally, this channel is involved in the production of the airways liquid layer and thus in the equilibrium production and physicochemical characteristics of mucus. In the case of cystic fibrosis, the deteriorated channels lead to a mucus of higher viscosity in various organs (e.g. lung, vas deferens, pancreas)[14].

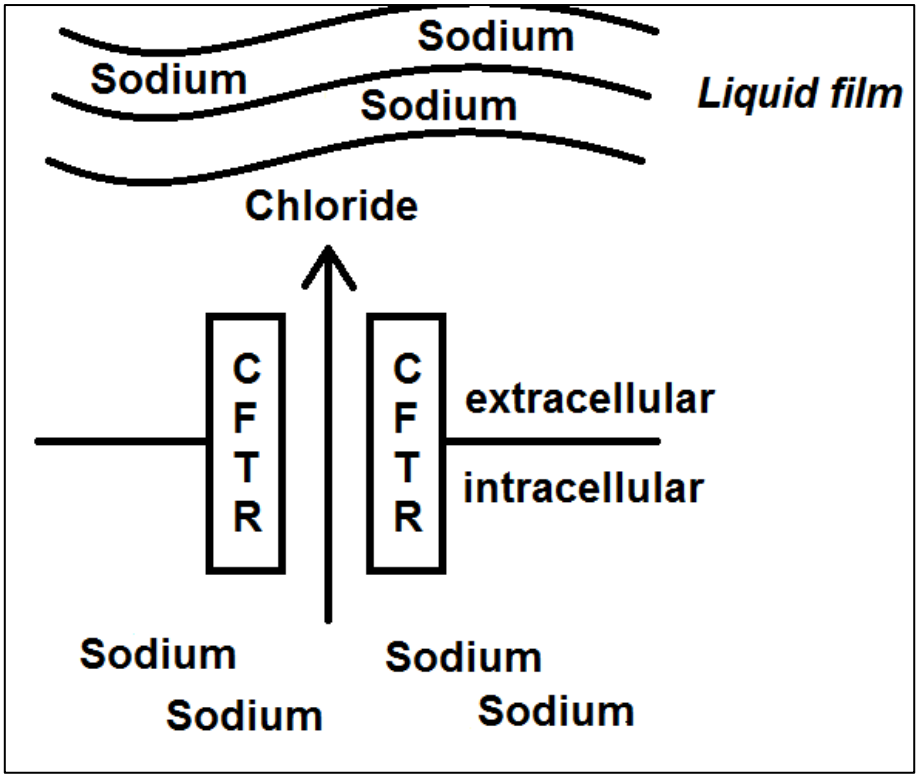


Fig. 1: *A normal functioning CFTR channel in a healthy person. Chloride is transported through the channel and combines with sodium to form salt (NaCl). The salt mixes with water to form a thin liquid film around the cell. Graphic adapted from "Mukoviszidose – Ursache, Krankheitsbild und Therapie" by Melichar & Hogardt.*[2]

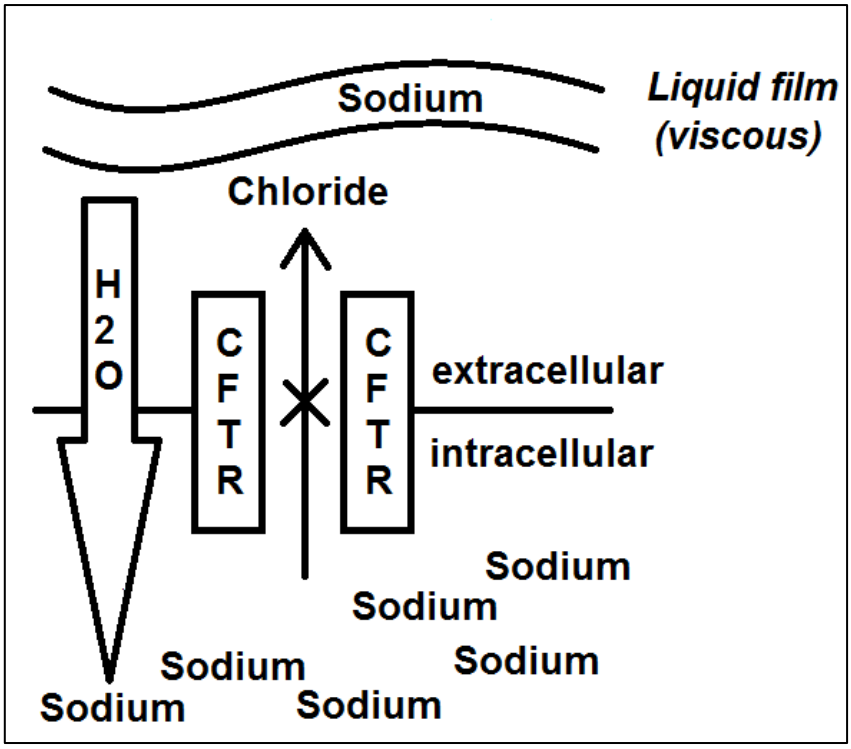


Fig. 2: *A dysfunctional CFTR channel in a patient with cystic fibrosis. Small quantities or no chloride can pass through the cell membrane. Decreased salt concentrations outside the cell are the consequence and higher salt concentrations are found inside the secretory cells. The water follows the salt gradient and migrates into the cell according to the osmotic principle. In sequel, the extracellular secretions have a decreased salt and water content, solidify, and become more viscous. Graphic adapted from "Mukoviszidose – Ursache, Krankheitsbild und Therapie" by Melichar & Hogardt.*[2]

Patients with class I-III mutations often show relevant pancreas insufficiency. In contrast, patients with class IV-V mutations often have sufficient CFTR function and are not pancreas insufficient[15]. Such a relatively close genotype-phenotype correlation has not been shown for the degree of the lung disease[7]. Other glands affected by the disease are the secretory glands in the skin, the intestine and the salivatory glands[16]. Another important repercussion of CFTR mutation could be the congenital bilateral absence of the vas deferens (CBVAD)[17], which results in the absence of the anatomic ducts through which spermatozoa pass from the testes to

the urethra. It leads to obstructive azoospermia and causes infertility in men. The congenital absence of the uterus and vagina (CAUV) has also been observed in CF patients[18]. Moreover, a minor problem is the modification of the lacrimal gland ductal secretion, which can lead to dry eyes[19-21]. A modification of the lacrimal gland ductal secretion was already shown in the mouse model[22].

1.3. Diagnosis of CF

1.3.1. Diagnostic standards

Early diagnosis of CF is important for early onset of therapy, a reduction of consequential damage, and a better prognosis. If no siblings are affected, further diagnostic steps are justified when clinical symptoms appear, including gastrointestinal symptoms (meconium ileus, fatty stools) and/or pulmonary problems[4]. The diagnostic tools often used are the sweat test, the CFTR mutation analysis and in vivo or ex vivo CFTR bioassays[23]. The last one is a physiological assay, which measures the epithelial ion fluxes at the mucosal surface by the voltage potentials created.

Sweat test: People with CF have more chloride in their sweat than healthy people. The diagnosis can be confirmed by showing a high chloride level and can be performed in children, when they produce enough sweat. The test should be done between 10 days and at the latest 4 weeks of age for babies, with a positive newborn screening or prenatal genetic test[24,25]. Sweat test values do not vary when a person grows older, has a cold or a brief illness. After placing an electrode containing pilocarpine and electrolyte solution, without interaction potential with the measurements of sodium and chloride at the test site, a second electrode is installed at another place. The pilocarpine will stimulate the skin and in particular the sweat glands after inducing a mild electric current, where positive tests will show a high chloride level. A chloride concentration above 60 mmol/L[23] confims cystic fibrosis. Between 30 and 59 mmol/L, CF is possible and additional testing is needed and the sweat test is repeated. If the newborn screening is positive, the sweat test falls

into the intermediate range, and if there is one or no CF causing mutation the result will be classified as CF related metabolic syndrome (CRMS)[25]. For results falling into the intermediate range with unknown mutations of the patients or undefined CFTR genotype further testing is recommended[25]. If further tests are neither available nor possible for other reasons, the patient may be considered to have CF related disorder. A chloride concentration of 29 mmol/L or lower in the sweat test indicates CF is unlikely, regardless of age. Patients with this result, a positive newborn screening and two CFTR gene mutations or, with at least one mutation which does not cause any physical CF symptoms, are classified to have CRMS.

By genetic testing, the diagnosis can be secured when mutations are found in both copies of the CFTR gene (homozygotic or compound heterozygotic). Missing mutations of this gene, however, by itself cannot exclude CF. The common test arrays only test for the most common mutations and other mutations have to be searched for with other techniques (gene sequencing)[4]. Furthermore, unknown mutations may exist and have to be taken into account. In summary, if the clinical presentation of a patient suggests CF, a stepwise approach has to be followed, starting with the sweat test and sometimes going to gene testing and physiological tests on mucosal cells. Measurements of potential differences in nasal or rectal mucosa were tested and are established for complicated or borderline cases[2326].

1.3.2. Extrapulmonary diagnostic

Extrapulmonary manifestations can also lead to CF diagnosis. Extrapulmonary symptoms can be a result of primary[4] CF manifestation such as exocrine pancreatic insufficiency, cholestasis, infertility or a result of secondary/late[4] complications such as endocrine pancreatic insufficiency, liver cirrhosis, or osteoporosis.

A meconium ileus occurs in 20% of patients and often is the first manifestation of CF[27]. The thickened and adhesive meconium obstructs the intestinal lumen. The simple and the complex meconium ileus are both described as major forms[28]. The viscous meconium leads to the obstruction of the terminal ileum and, with the intes-

tinal tract still intact[27], the proximal parts of the small intestine become dilated with additional gas, fluid and meconium for simple meconium ileus forms[27], which appear immediately at birth[29]. In utero genetic diagnosis of CF and ultrasound of the abdomen enable an early diagnosis, bilious vomiting and failure to stool are further indicators. Complex meconium ileus presents earlier in utero and sometimes postnatally[29]. Severe complications like atresia, prenatal volvulus, ischemic necrosis or perforation have been described, sometimes with pseudocyst formation and extrusion of the meconium into the peritoneum[27].

There are many mucus or secretory cells in the digestive tract. In CF, the mucus or the liquid produced is too viscous. This is particularly unfavorable for the exocrine pancreatic functions. The viscous pancreatic juice clogs the fine ducts in such a way that little or no secretions get into the intestine. The pancreatic exocrine secretions are necessary to digest food into absorbable nutrients; if the food is not digested by these pancreatic secretions, it cannot be absorbed in the small intestine and all nutrients and calories get lost. Sugar, fat and protein proceed into the large intestine. There, these nutritional components are broken down by the bacteria of the intestinal flora. This causes flatulence and greasy shiny stools or diarrhea and abdominal pain. About 85% of the CF population is pancreatic insufficient before one year of age[30]. This is why untreated CF patients do not thrive normally. Endocrine function is affected later[31], but around 20 % of adolescents and later, 40-50% of adults develop CF related diabetes. This type of diabetes occurs 6 years[32] after an impaired glucose utilizeation can be demonstrated[31] and increases mortality in CF patients.

A dysfunction of CFTR channels lead to cholestatic liver disease. Reflux of viscous bile, which is also hyper-viscous in CF patients, can result in inflammation of the bile ducts[33] and the liver with subsequent periportal fibrosis[34]. Liver alterations comprise different forms and levels such as steatosis or primary sclerosing cholangitis (PSC). Signs of steatosis are found in almost 60% of patients[35,36] and CF liver disease including focal biliary cirrhosis and portal hypertension in just below

30%[35,36]. Moreover, if the bile flows too slowly into the intestine, the absorption of fat from the food is inefficient and the stool turn beige-white causing steatorrhea.
CF liver disease is the third mortality cause in CF patients only surpassed by lung and transplantation complications. Fibrosis of the liver and liver cirrhosis are major findings[34] in CF patients, necessitating regular monitoring of the liver function to counteract any change or deterioration in condition.

Due to the above-mentioned viscous consistency of the seminal fluid, but also because of abnormalities in the vas deferens and epididymis, fertility is reduced in approx. 90% of male CF patients[17]. Thanks to newer urological methods and assisted reproductive techniques[37], these problems can be circumvented. In women, decreased mucus formation and the formation of clots in the fallopian tubes makes pregnancy considerably more unlikely[18]. Pregnancy, however, is feasible in CF patients but needs intensified monitoing and support to lower the associated risks[38].

1.3.3. Monitoring

According to guidelines, patients should first be assessed and discussed in a multidisciplinary team[39] and all aspects of CF care have to be evaluated, including assessment of competence of airway clearance and inhalation technique. Clinical assessments should be performed at least every 3 months and, in addition to this, at times of symptomatic deterioration[40]. At every clinical visit, airway cultures, including typical CF pathogens, have to be obtained to monitor and control airway infection as major driver of CF lung disease[41]. Drug interactions and therapy (for example for CFTR modulator therapy: liver function testing, assessment for childhood cataract)[39] have to be monitored. Another aspect of clinical monitoring of CF is lung function testing. Usually, patients able to cooperate (over 5 years old)[40] should be examined making use of spirometry or bodyplethysmography. Pre- and post-bronchodilatator test results according to ATS/ERS criteria should be available[42].

A summary of diagnostics for CF patients is given in the two tables below. The guidelines are taken from “Standards of care”[43] and “Klinische Pneumologie”[4].

Pre clinical	-History (including vaccination status, allergies, previous illnesses, family history, and smoking history)
Clinical examinations	-Physical examination including anthropometry (height, weight, BMI calculation) -Sputum culture -Pulse Oximetry -Spirometry
Laboratory requirement	-Differential blood count -Inflammation markers (e.g. C-reactive protein, BSR, IgG)

Table 1: *Diagnostics that have to be done in CF Patients every 3 months*

Clinical examinations	-Bodyplethysmography -Capillary blood gas analysis** -Chest X-ray (in two directions in adults) -Abdominal sonography -Oral glucose tolerance test (10 years of age and older) -Ergometry (over 10 years old: tread-mill; parts with limited gas exchange: 6-minute walk) -Bone density measurement (female over 12 years old and male over 13 years of age: every 1–2 years, e.g. by DEXA scan) -Transthoracic Echocardiography (TTE) -Nutritional advice (if necessary, 24-hour stool fat determination, elastase I in the stool) -Checking physiotherapy (including checking the nebulizer technique) -Contact with psychologist / social counseling
Laboratory requirement	-Electrolytes (Na+, K+, Cl-, Mg2+, Ca2+, Phosphate) -Kidney function (creatinine, urea, uric acid, creatinine clearance)** -Liver function (SGOT, SGPT, AP, γ-GT, CHE, GLDH, total bilirubine)** Coagulation analysis (INR, PTT, thrombine time, fibrinogen)** -Immunoglobulins quantitatively (IgG, IgE), Aspergillus antibodies, RAST +

	precipitins, PSA antibodies*** -Vitamin E, D, A, β-carotene -Lipase / amylase, blood sugar / HbA1c** -Iron status (iron, ferritin, transferrin, TIBC) -Urine status / sediment
* In case of an exacerbation, has to be donor earlier or more frequently ** With known organ dysfunction (lung, liver, kidney, and/or pancreas) more frequently, e.g. with routine presentation every 3 months *** In case allergic bronchopulmonary aspergillosis (ABPA) has to be considered	

Table 2: *Diagnostics that have to be done in CF Patients every year.*

1.4. Therapy of CF

Cystic fibrosis is not contagious; however, CF patients can be infected more easily than other people with certain germs from the environment. In particular, bacteria, viruses and fungi in the airways cause larger damage in CF patients and have more chances to persist (chronic colonization). Therefore, CF patients have to take certain hygiene measures in a preventive manner. These habits include regular, thorough hand washing, because most germs are transmitted through the hands. Moreover, CF patients have to take special hygiene measures in the home environment to avoid germs that can be found in respiratory therapy equipment used[44] or in wet rooms (e.g. P. aeruginosa)[45] to make sure they cannot enter the airways.

Different approaches exist to treat cystic fibrosis. One of the most important pillars of the comprehensive therapeutic approach is drug therapy. Other elements of therapy approaches such as dietary support[46,47], physiotherapy, rehabilitation[48], and sports[48] should not be underestimated and can help to improve functional performance, prognosis, and quality of life of CF patients.

1.4.1. Drug and inhalation therapy

Drug therapy consists of five different categories: mucolytics, anti-inflammatory drugs, medication against infection, digestive enzymes, and a new group of the CFTR modulators.

The viscous mucus in the lung has to be liquified to alleviate symptoms and sequelae. Therefore, expectorant drugs are used for inhalation therapy. The mucus becomes more fluid by adding water (for example through inhalation of sodium chloride solution[49,50], also called hydrator) and the decomposition of sticky components in the slime (for example by means of the inhalation of DNase). That way, the mucus can better be removed from the lower airways and coughed up. Dornase alfa[51] has a proven efficacy in CF treatment. Other options are inhalation of hypertonic saline[52] or mannitol[53,54], osmotics which improve lung function by drawing water into the airways and improving airways epithelial lining fluid viscosity[55].

Persistent inflammation damages the lung tissue. Inflammation can be suppressed with medications such as corticosteroids or ibuprofen[56]. If the inflammation is caused by bacterial or other infections, antibiotics and other anti-infective drugs are used.

Infections of the lungs with bacteria, viruses or fungi are treated with antibiotics, antivirals or antifungals respectively. Long time treatment with antibiotics are mostly delivered to the airways by nebulizer therapy. Alternatively, they can be given in form of tablets or in the case of pulmonary exacerbations they can be administered intravenously. Three different types of airway infections are known: an early, an intermittent and a chronic type of infection[39]. Inhaled antibiotic therapy is being used to reduce the amount of pulmonary bacterial load and reduce the number of exacerbations[57] as part of a long-term therapy[50] when different antibiotics are alternated or a single antibiotic can be used on a long term basis[39]. Macrolid antibiotics are often used because of their anti-inflammatory and antimicrobial effects. They are particularly effective in the treatment of chronic P.

aeruginosa infection, when the bacteria reside in biofilms[39,58]. Maintenance therapy of chronic P. aeruginosa infection in CF patients is recommended with azithromycin[59]. Unfortunately, the bacteria can develop resistance to the antibiotics used and may require to administer more potent or reserve antibiotics such as colistine. For the treatment of pulmonary exacerbations due to bacterial infections intravenous antibiotic treatment is indicated[58]. Especially patients with advanced CF lung disease (ACFLD), according to the multidisciplinary Cystic Fibrosis Foundation committee recommendation, often acquire resistant organisms[60]. They are frequently subject to exacerbations and in consequence need intravenous antibiotic treatment more often. This is one factor which may explain why the necessity of intravenous antibiotic treatment correlates with a decreased lifetime prognosis[61].

To ensure digestion of food in the intestine, cystic fibrosis patients with pancreatic insufficiency have to take digestive enzymes with every meal. The amount of enzymes needed must be calculated to match the respective food, according to international guidelines[62,63]. This individualized dose calculation has to be explained to the CF patient in nutritional counseling, which should be a regular part of therapy.

The CFTR modulators and potentiators are a new type of CF drugs. They make the CFTR channel work better and can solve the problem of the viscous film produced. The precise recommendations depend on age, gating mutations and FEV1%[64] since these drugs are extremely expensive and are working on a mutation specific principle. The advent of these therapies has been a milestone in history of cystic fibrosis therapy, but so far, the effectiveness is not wide spread enough that other therapies such as inhalation and digestive enzymes would no longer be necessary. CFTR modulators act by potentiating and correcting the protein expression of CFTR channels. Two main preparations called Lumacaftor and Ivacaftor have a demonstrated clinical efficiency. Lumacaftor is a corrector of intracellular trafficking of CFTR, helps the F508del-CFTR protein form the right shape[65] and prevents premature cytosolic degradation of CFTR[66]. Ivacaftor is a CFTR potentiator, binds to the defective protein at the cell surface, opens the chloride channel so that chloride can flow through and increases the residual activity of de-

fective CFTR proteins[67]. Both drugs have been shown to improve lung function and reduce pulmonary exacerbations significantly[68,69]. There are all in all four CFTR modulators[65]; Ivacaftor (Kalydeco®), Lumacaftor/Ivacaftor (Orkambi®), Tezacaftor/Ivacaftor (Symdeko®), Elexacaftor/Tezacaftor/Ivacaftor (Trikafta™, not approved in the European Union). Tezacaftor acts in the same way that Lumacaftor does, but has fewer side effects in combination with Ivacaftor[65]. Elexacaftor helps the F508del-CFTR protein form the right shape and corrects an additional flaw[65] in the protein formation. The cellular transport mechanisms for ions and liquid are complex. A large number of additional other channels have been discovered and have been shown to have effects on membrane potentials, membrane interactions and CF pathology. Most of them regulate the secretion and absorption of chloride ions and have a main role in the actual aspects of today´s research[70,71].

1.4.2. Nutritional therapy

CF patients need an effective and adequate nutritional therapy based on the mismatch between increased resting calorie needs and low energy absorption due to malabsorption. The maldigestion that occurs in most cystic fibrosis patients can be solved by taking digestive enzymes. Moreover, a balanced and high-energy diet for CF patients is particularly important. The lung obstruction goes hand in hand with an increased energy amount required for breathing and coughing. Infections, fever and diarrhea also consume a lot of energy, the demands of which are significantly higher than for healthy persons. The water and sodium chloride losses have also to be balanced and necessitate an increased contribution of fluids and salt. CF prognosis is strongly associated with the nutritional status and the BMI[72]. BMI but also vitamins, as well as trace elements should be monitored. A BMI in excess 20 kg/m² is recommended, ideally of 22 kg/m² for women with CF and 23 kg/m² for men with CF[73].

1.4.3. Physiotherapy

Regular physiotherapy is a cornerstone of cystic fibrosis therapy. Here, cystic fibrosis patients learn to use the cough productively and cough up tough mucus and stretch her chest. The breathing and stretching exercises must be done daily and start in infancy. The goals are the mobilization and elimination of the retained secretion, a relief of the auxiliary respiratory muscles and the preservation of chest mobility. Different passive (e.g. muscle stretching, skin- and connective tissue techniques, manual vibration) and active (e.g. self drainage, oscillation techniques) therapy procedures exist. They are in particular effective in combination with mucolytic and bronchodilator inhalation therapy[74].

1.4.4. Sports

Physical activity and sports have a positive impact on the health of CF patients. They help to improve lung function, combat breathlesness[75], and the flexibility of the chest. In addition, physical exercise has a positive effect on bone strength, the coordinative skills, posture and physical performance[76]. CF affected people can improve their performance through targeted training. Not every sport is equally suitable for CF patients. A combination of physiotherapy and fitness training shows a high degree of evidence for a better outcome and benefits for CF patients[77-79]. Different sports such as bungee, rugby, parachute jumping, skiing and scuba diving however are not recommended for CF patients[80]. During sports activities, the patients have to rehydrate themselves regularly and to replenish the body with salt and water, in particular for endurance sport due to excessive salt and water losses by sweating. Furthermore, exhaustive sports activities during infective exacerbations are highly disadvised[80].

1.4.5. Lung transplantation

Lung transplantation may be an opportunity for CF patients to be able to continue living if the lung is so severely damaged that it will no longer fulfill the tasks of sufficient oxygen uptake and carbon dioxide release. In CF, most patients will receive bilateral transplantation. The donor lung not having cystic fibrosis gene mutations can function normally in the body of the CF patient. Cystic fibrosis will not reappear in the transplant because of the normal genetics of the tissue. Nevertheless, a transplantation involves many risks and the mean duration of sufficient function of the transplanted organ is in the range of 10 years. It is hard to predict on an individual basis which patient will have an improved overall survival after transplantation, quality of life, though, is significantly improved in the majority of cases[81]. After a bilateral transplantation, the mean 3-month survival is close to 90% - even higher in large capacity transplant centers -, the 1-year survival 81% and the average long-term survival is limited to a median of 5.6 years, depending on the careful selection of recipients and the size and the experience of the transplant center[82]. Major complications are chronic allograft dysfunction syndrome, i.e. bronchiolitis obliterans syndrome, infections, immunosuppression induced malignancy, and lymphoproliferative diseases[82,83].

1.4.6. Rehabilitation

Inpatient rehabilitation in qualified facilities plays an essential role in the treatment of CF patients, rehabilitation goals being stabilization of the patient condition and, if possible, also to improve health and quality of life (i.e. reaching medical goals such as improving body weight and resilience as well as the reduction of the consequences of infections of the lungs and respiratory tract). The next essential step, where rehabilitation has an important role is the restoring of participation in social and professional life. Many CF patients know the advantages and profit from the benefits of inpatient medical rehabilitation in specialized clinics[84,85]. Intensive therapy under the supervision of a multi-professional team[86], the chance to find courage by meeting other CF patients and get new suggestions is of great value. Re-

duction of cough and/or shortness of breath, improved physical activity with gain in physical fitness, better sleep, and general health perception as well as better integration of therapy into daily routine, enjoying leisure activities again, and being free from anxieties was noted after inpatient rehabilitation[84].

There are various offerings for adults, for adolescents, and children (with and without accompanying person) or for the whole family. In this case it´s called "family-oriented rehabilitation" measure (FOR)[87]. This type of therapy is especially utilized for diseases of the chronically ill patient, not just for CF patients[88]. Exchange with the CF outpatient clinic in advance of the rehabilitation is highly recommended and helps to set individual rehabilitation goals (e.g. increasing physical resilience, improving secretion mobilization).

1.5. Surrogate markers of prognosis in CF

Previous work has shown that prognosis in CF is related to Body-Mass-Index (BMI)[89], Forced Expiratory Volume in 1 second (FEV1)[90], and need of intravenous antibiotic therapy [43]. This is why these three parameters are recommended to be measured and monitored regularly. They have significant impact on survival and on the quality of life of CF patients [91]. Disease progression in cystic fibrosis (CF) is marked by deterioration of a number of physiological indicators [91], especially lung function is affected[43] progressively leading to pulmonary damage and in a final state, to respiratory failure. This is the consequence of a impaired mucociliary clearance. The cilia of ciliated airways cells together with airways geometry are normally responsible for transport of mucus located in the deeper airways towards the mouth, but in CF they cannot efficiently clear the airways because of the high viscosity of the mucus and additional inflammatory damage. This malfunction of the mucociliary clearance of the airways cannot be compensated by coughing and it leads to mucostasis[92] and consequently to inflammation and a higher rate of infections, bronchial wall destruction i.e. bronchiectasis, emphysema and loss in pulmonary function (FEV1, FVC, hyperinflation, increased airways resistance, hypox-

emia, and pulmonary hypertension). Moreover, in the upper airways, sinusitis and polyposis nasi can cause additional problems.

The cardiovascular system in CF shows signs of chronic overload i.e. pulmonary hypertension, cor pulmonale, right heart failure, and portal hypertension is a common problem. Gastrointestinal manifestations of CF are frequent. Liver cirrhosis is common (fatty liver, periportal fibrosis, biliary cirrhosis, cholecystolithiasis, cholangiolithiasis), the pancreatic dysfunction causes maldigestion, recurrent pancreatitis, islet cell insufficiency and CF-related diabetes). The intestine plays an important role in the overall health situation of CF patients with meconium ileus being the most prominent and early manifestation and malnutrition and vitamin deficiency being very common, while rectal prolapse and ileum invagination is rather rare. Also urogenital problems can occur. In some patients with nephrolithiasis or amyloidosis with impaired kidney function, infertility is a commonly found problem amongst males. Bone, muscle and joint problems are also possible CF manifestations with osteopenia, skeletal deformity, arthritis, atrophic skeletal muscles and hypertrophic auxiliary breathing muscles.

1.6. Our Study/ Background

In July 2018 the two centers of the Pulmonology Scientific Research Institute, Moscow and the University Hospital Frankfurt (Christiane Herzog CF-Zentrum) started a collaboration. Both centers care for CF-patients, children as well as adults.

A retrospective descriptive study was started after **approvement (pages 114-115) by the ethics committee** to look for differences between patients treated in the Moscow CF center and the Frankfurt CF center from 1990 to 2015. The question was whether there was a significant and relevant difference and if so, would this be visible in a difference of three indicators (BMI[89], FEV1[90] and the necessity of intravenous antibiotic therapy caused by exacerbations in CF[61]) serving as surrogate markers of prognosis. BMI can be compared in stratified age classes. Higher BMI

is related to better lung function test results (which improves consequently quality of life and survival) and in particular for underweight individuals a poorer prognosis has been reported[89]. FEV1 is the second parameter used to mark progression of CF lung disease and to evaluate therapeutic efficacy[90]. Furthermore, FEV1 can be used as prognostic tool for mortality[90,93-95]. Need of intravenous antibiotic therapy as a result of a severe pulmonal exacerbation[61] or P. aeruginosa infection[96] has been used as a third marker for the prognosis in CF[61,96]. Exacerbations have a high impact in terms of current morbidity as well as implications for long term morbidity and mortality[61,94]. Presence of P. aeruginosa is associated with higher rates of lung function decline in all age groups[96]. Utilization of intravenous antibiotic therapy can be used to identify cases where an infectious exacerbation has been clinically diagnosed, and thus can be used as a surrogate marker for infection.

No comparable study between German and Russian CF patients has been published so far, i.e. we are not aware of any comparative study in CF patients in this setting in the past.

2. Materials and methods

2.1. German patient data

German patient data were collected from the German national CF registry "muko.web"[97] after approvement by the ethics committee. This registry was started 1995 under the name "Qualitätssicherung Mukoviszidose" and has later been renamed into "muko.web". In the year 2015, ninety German CF centers took part in data gathering via Muko.web, describing 5331 patients in much detail (median age 20; 56.5% adults; 51.8% men; 80 died in 2015; median dying age 32)[97]. Data collected from muko.web for the study were height, weight, BMI, FEV1, Forced Vital Capacity (FVC), year of birth, year of death, gender and P. aeruginosa presence. In addition to these, date of diagnosis of P. aeruginosa infection of CF-patients in Frankfurt from 1990 to 2015 were retrieved. These data were anonymized and gathered into an Excel table. Missing values - in particular those describing the

utilization of intravenous antibiotic therapy (not listed in muko.web) - were completed with data from the Hospital Medical record Information System (Orbis, Agfa) of the Frankfurt University Hospital. German patients were coded with the letter “f” and were assigned to group 01. They received a three-digit numerical code “XXX”.

2.2. Russian patient data

Russian patient data were collected directly from the medical files of the Pulmonology Scientific Research Institute, Moscow of the FMBA (Federal Medical-Biological Agency) of Russian Federation. Collected data were anonymized and regrouped in the same standardized table as in Frankfurt. Russian patients were coded with the letter “m” and were assigned to group 02. In the same way as in Frankfurt they received a three-digit numerical code “XXX”.

2.3. Grouping of data

With this anonymized code data of both centers were aggregated in one data table. Gender information was coded with 01 for male patients and 02 for female patients. Body weight was expressed in kg (kilograms), body height in cm (centimeters), FEV1 in mL (milliliters), FVC in mL (milliliters). The presence of P. aeruginosa was coded with 01, the absence of P. aeruginosa with 02. Necessity of intravenous antibiotic treatment received the code 01 (02 coded no need of intravenous antibiotic treatment).

2.4. Data analysis with Bias and R-Studio

The complete data were biometrically analyzed with the program “Bias”[98]. After a descriptive approach of complete data, differences in BMI and FEV1 values were observed. Exemplarily, BMI in the two centers was compared for 2015 after separating the sample in age classes[99,100]. FEV1 is an inconstant value, as it depends on age, height, and gender[101,102]. To compare FEV1 between both centers in 2015, a script was written in Rcode and executed with R-Studio – a statistical programming tool, which can execute Rcode and analyze statistical data -. MatchIt[102] was

used to create two new comparable samples. Data pairs were matched according to the parameters influencing FEV1 (height, age, gender)[101,103]. The size of both samples was 100 patients and both samples were statistically not significantly different concerning height, age and gender (before matching p<0,001, after matching p=0,484). Both matched samples were compared for their FEV1 values in a new statistical biometrical analysis with "Bias"[98].

2.5. Comparison to normal population

Data of the study were compared to normal population data in Germany[104] and the Russian Federation[105-107] taking into account differences in age distribution, which are known influence CF-patient data. Especially societal differences in the normative expectations of BMI and actual BMI in the normal population of both countries may have an influence on samples taken in the resp. CF populations.

2.6. Comparison of standards of care in both centers with CF guidelines

To evaluate potential differences found, we decided to compare the standards of care for CF patients in Frankfurt and in Moscow. Therefore we took the Kerem[43] CF standards of care as comparison scale. The standards of care were raised according to internal instructions and interviews with local experts.

3. Results

3.1. Description of the data range: Age

The study totalized 428 (72.91%) patients from Moscow and 159 (27.09%) patients from Frankfurt, which summed up to a total of 587 analyzed patients. All of them were born in 1999 or earlier. The oldest patient of this study was born in 1949.

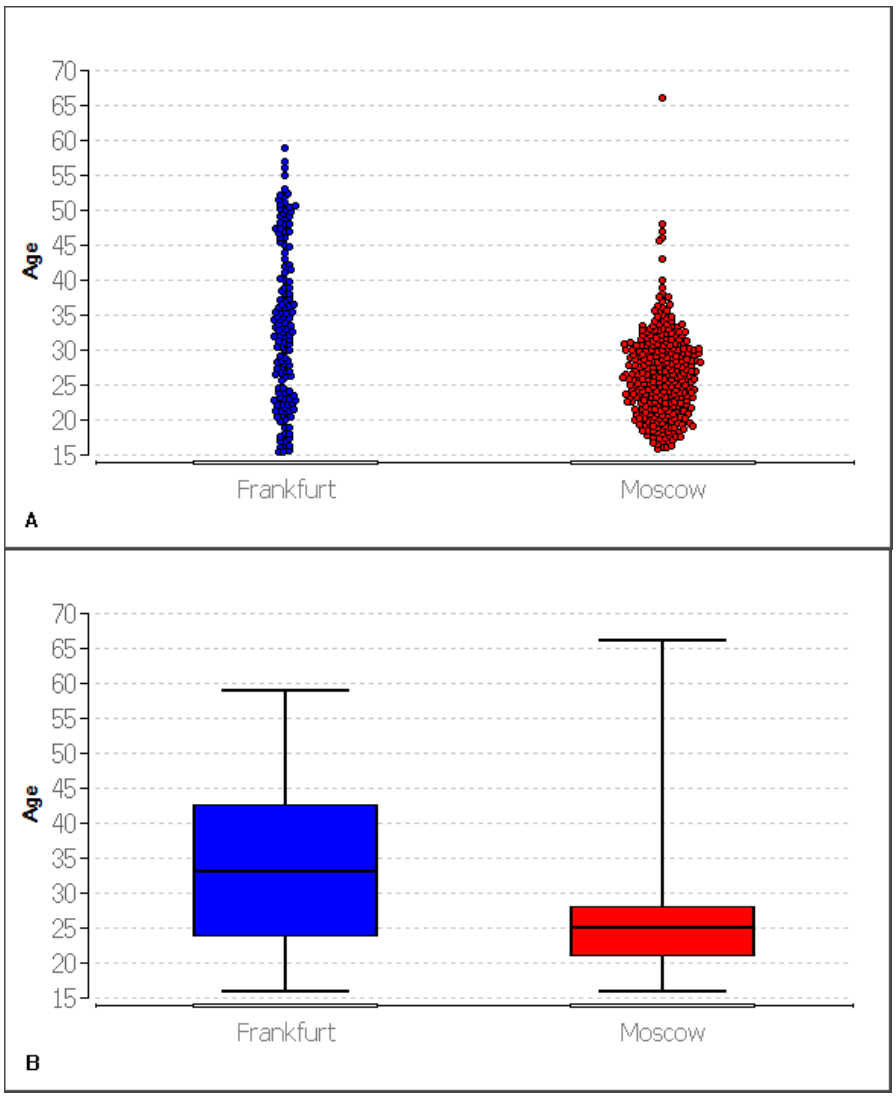


Fig. 3: *Differences in age in both CF-populations.*

A) *Age distribution of CF-patients in both centers described in dot plots.*

B) *Box plot of patients' age representing median, first quartile and third quartile.*

Average[108] age was 33.57 for Frankfurt, 25.59 for Moscow and for the total cohort 28.14. Standard deviation[108] was 11.27 for Frankfurt, 6.10 for Moscow and 8.92 for total cohort. Median[108] age was 33 for Frankfurt (1st quartile 24 years, 3rd quartile 42 years), 25 for Moscow (1st quartile 21 years, 3rd quartile 28 years) and 26 for total cohort (1st quartile 22 years, 3rd quartile 32 years). In both centers minimum age was 16 (so same for total cohort). Maximum age in Frankfurt was 59 years. In

Moscow it was 66 years (consequently 66 years for total cohort). Finally range was 43 years for Frankfurt and 50 years for Moscow and total cohort. We can observe the Russian cohort is significantly younger than the German cohort.

3.2. Description of the data range: Gender distribution, P. aeruginosa presence and more

In Moscow 217 (50.70%) male patients and 211 (49.30%) female patients were counted, while in Frankfurt 92 (57.86%) male patients and 67 (42.14%) female patients were registered. A performed Chi-square test with Yates´s correction for continuity[108] confirms both samples are comparable (p=0,147) for gender distribution.

348 (81.31%) Moscow patients were infected with P. aeruginosa and 80 (18.69%) were negative. In Frankfurt the number of P. aeruginosa infected patients was 137 (86.16%) while 22 CF patients were not infected (13.84%). In the same way as for gender distribution a Chi-square test with Yates´s correction for continuity[108] was performed (p=0.209). Subsequently both CF-patient populations were comparable for P. aeruginosa positivity (p=0.209).

Six (3.77%) patient deaths were recorded in Frankfurt (0 until 2015) and 114 (26.64%) recorded patients died in Moscow (68 (15.89%) until 2015).

3.3. Description of the data range: BMI, FEV1 and necessity of intravenous antibiotic therapy evolution over time

Data were statistically analyzed and important values were calculated and entered into Table 1. Key values of BMI, FEV1 and necessity of intravenous antibiotic therapy were examined.

Examination	Number of Patients		Average BMI		Median BMI	
Year	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	2	0	21.52	-	21.52	-
1991	2	1	21.54	14.49	21.54	14.49
1992	1	2	21.50	16.27	21.50	16.27
1993	2	7	20.91	16.44	20.91	15.08
1994	1	11	20.02	17.34	20.02	17.16
1995	10	7	16.66	17.36	16.11	17.16
1996	30	10	18.84	16.91	18.52	17.39
1997	35	23	19.41	17.61	19.55	17.72
1998	46	38	19.89	16.34	19.66	16.45
1999	45	39	19.97	17.33	19.13	17.65
2000	30	45	20.29	16.98	19.09	16.53
2001	14	53	19.07	16.79	18.05	16.85
2002	16	64	18.78	17.41	18.02	17.54
2003	68	78	21.43	17.42	20.85	17.55
2004	75	103	21.48	17.49	20.76	17.57
2005	13	101	20.57	18.04	20.68	18.03
2006	13	124	20.95	18.02	21.27	17.96
2007	13	160	20.51	18.11	21.10	18.13
2008	91	179	21.69	18.38	21.01	18.55
2009	84	188	22.39	18.55	21.81	18.52
2010	132	192	21.20	18.76	20.70	18.69
2011	137	199	21.40	18.71	21.14	18.47
2012	131	250	21.80	18.79	21.62	18.51
2013	130	263	21.99	18.68	21.66	18.29
2014	133	278	22.12	18.78	21.73	18.52
2015	141	301	22.24	18.74	21.63	18.59

Year	BMI standard deviation (SD)		BMI maximum		BMI minimum	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	0.64	-	21.98	-	21.07	-
1991	1.13	-	22.34	14.49	20.75	14.49
1992	-	1.75	21.50	17.51	21.50	15.03
1993	1.26	2.88	21.80	20.93	20.02	13.22
1994	-	3.82	20.02	25.00	20.02	13.34
1995	2.29	2.37	20.64	22.21	13.68	15.43
1996	3.17	2.21	25.83	19.37	14.07	13.47
1997	3.18	2.49	28.22	22.77	13.71	13.34
1998	3.18	3.58	27.64	22.77	13.65	1.92
1999	3.52	2.51	31.11	22.94	14.88	12.63
2000	4.89	2.71	37.56	24.15	13.13	12.70
2001	4.02	2.69	27.76	22.76	14.60	12.40
2002	2.94	2.65	24.01	23.23	14.74	11.65
2003	3.76	2.70	33.30	23.61	13.98	11.65
2004	4.05	2.77	35.50	24.88	12.93	10.82
2005	3.22	2.76	26.35	25.86	13.73	12.02
2006	3.35	2.83	26.67	25.72	14.38	12.03
2007	3.58	2.73	24.97	25.62	13.89	12.73
2008	4.10	2.79	40.75	26.23	14.38	11.83
2009	4.41	2.78	44.29	26.03	15.34	12.80
2010	4.20	2.84	45.35	30.03	14.27	12.60
2011	4.18	2.90	45.52	31.99	14.35	12.47
2012	4.03	2.69	45.34	27.73	13.86	12.47
2013	4.04	2.80	44.47	27.73	13.86	10.85
2014	4.17	2.86	45.41	31.46	14.10	13.02
2015	4.13	2.78	46.60	31.46	14.17	11.33

Year	BMI range		BMI 1st quartile		BMI 3rd quartile	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	0.91	-	-	-	-	-
1991	1.59	0.00	-	-	-	-
1992	0.00	2.48	-	-	-	-
1993	1.78	7.71	-	14.49	-	18.42
1994	0.00	11.66	-	14.22	-	19.30
1995	6.96	6.78	15.21	15.64	17.29	17.70
1996	11.76	5.90	16.51	15.35	20.88	18.85
1997	14.51	9.43	17.38	15.89	20.87	19.12
1998	13.99	20.85	17.93	14.22	21.60	18.46
1999	16.23	10.32	17.79	15.41	21.72	19.00
2000	24.43	11.45	17.59	14.81	21.15	19.23
2001	13.16	10.36	15.90	14.66	21.14	18.67
2002	9.27	11.58	16.76	15.23	21.38	18.93
2003	19.33	11.96	19.03	15.23	22.92	19.11
2004	22.57	14.06	19.23	15.21	23.00	19.47
2005	12.61	13.85	19.33	16.37	22.01	19.68
2006	12.29	13.69	19.76	15.66	22.60	19.82
2007	11.08	12.89	20.48	16.28	22.92	19.91
2008	26.37	14.40	19.58	16.47	22.80	20.09
2009	28.95	13.22	20.03	16.71	23.46	19.93
2010	31.08	17.43	18.81	16.97	22.95	20.20
2011	31.17	19.53	19.05	16.93	23.13	20.45
2012	31.48	15.27	19.34	16.86	23.29	20.45
2013	30.61	16.88	19.58	16.82	23.69	20.43
2014	31.32	18.44	19.31	16.86	23.81	20.50
2015	32.43	20.13	19.31	16.82	24.14	20.32

Table 3: *BMI biometrical descriptive statistics from 1990 to 2015 including number of patient data sets, average BMI, median BMI, SD (standard*

deviation) BMI, maximum BMI, minimum BMI, BMI range, 1st quartile BMI and 3rd quartile BMI.

Data were statistically analyzed and values were calculated and entered into Table 1. Key values of BMI, FEV1 and necessity of intravenous antibiotic therapy were examined. In summary the parameters in Table 1 are mostly closer to normal for Frankfurt patients than for Moscow patients. From 1990 to 1995 there were not sufficient data and consequently values and results cannot be considered to be representative. FEV1 values have to be corrected by height, age and sex category[101,103], therefore, they are not directly comparable (for full data, see appendix, Table 10).

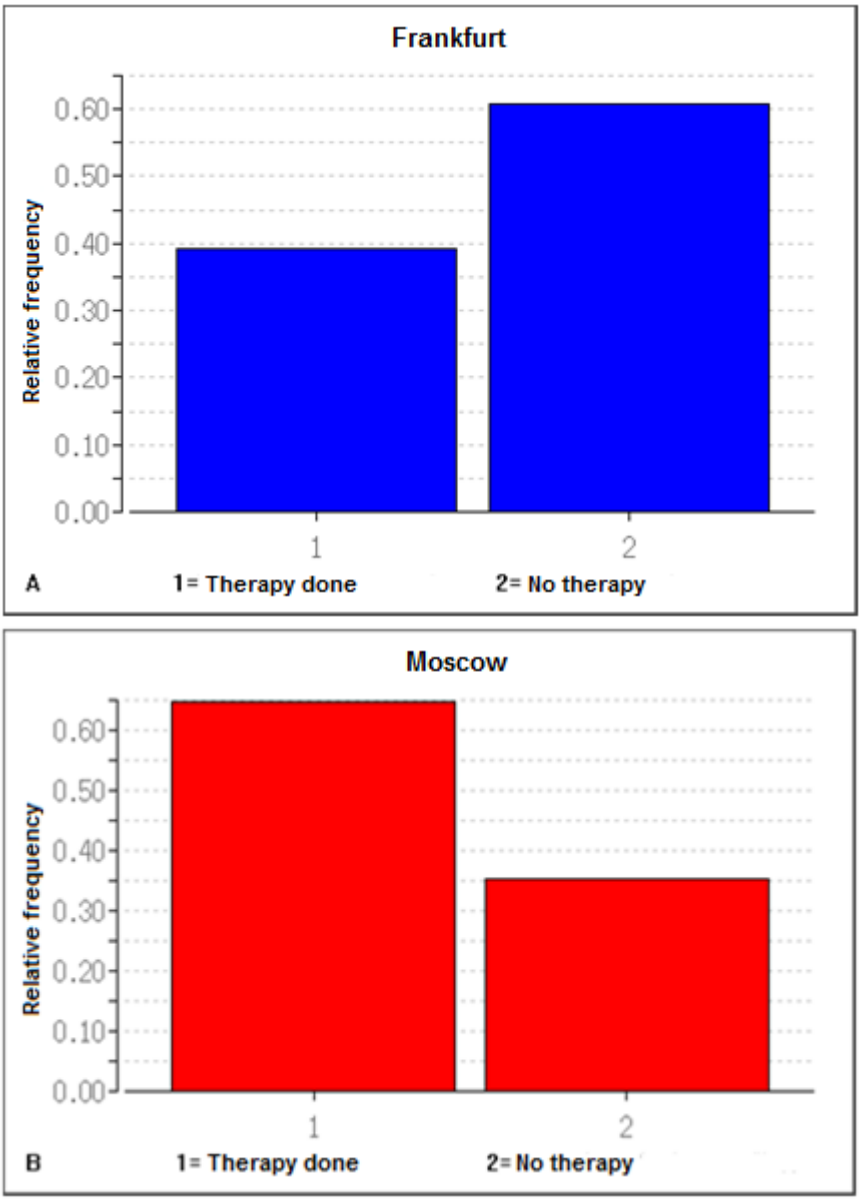


Fig. 4: ***A)*** *Intravenous antibiotic therapies in Frankfurt in 2015 (relative frequency). 1= Therapy done; 2= No therapy.*

B) *Intravenous antibiotic therapies in Moscow in 2015 (relative frequency). 1= Therapy done; 2= No therapy.*

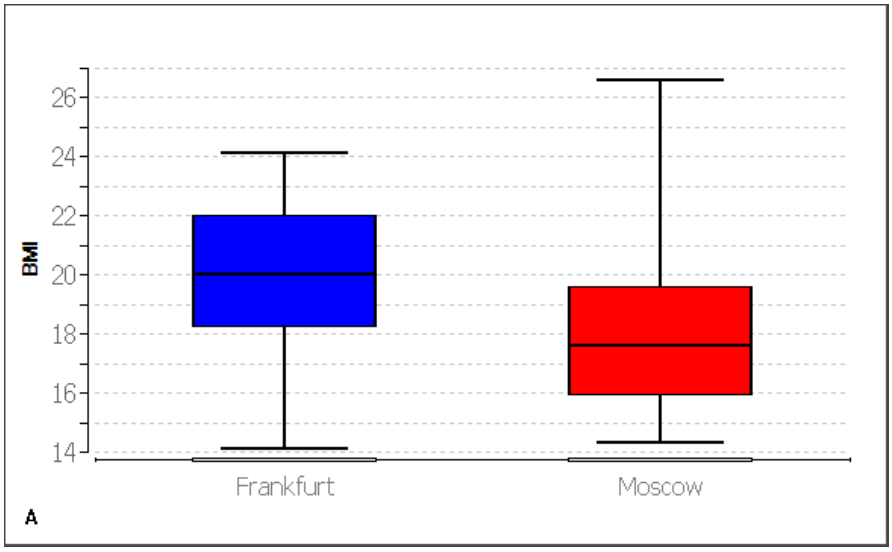
Intravenous antibiotic therapies in Moscow were carried out more frequently than in Frankfurt in 2015. Intravenous antibiotic therapies are usually done to treat pulmonary exacerbation in CF patients and frequency correlates with number of exacer-

bations. These differences, however were not statistically significant over a longer period of observation(p>0,1).

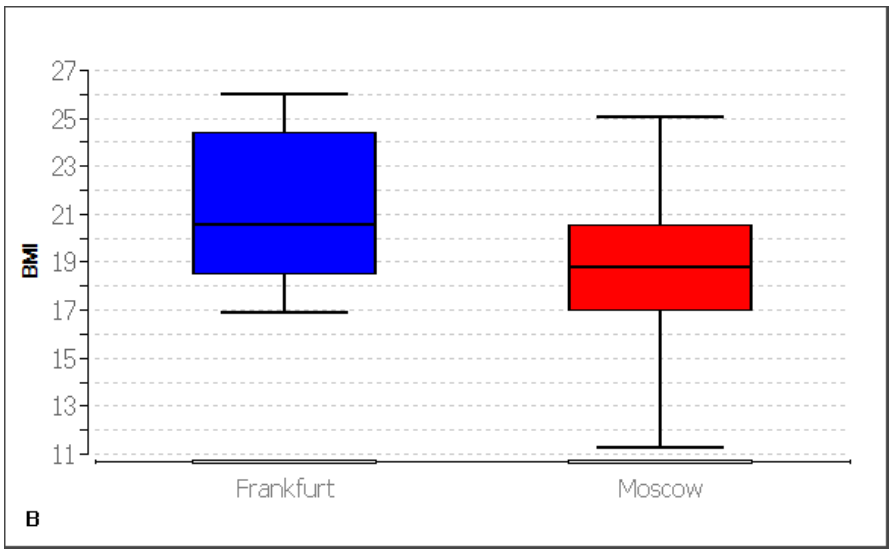
3.4 Comparison of BMI in both CF populations in 2015

To evaluate if there was a significant statistical difference in BMI between patients in Frankfurt and Moscow, the data set of the year 2015 was analyzed exemplarily. Patients were categorized in age groups.

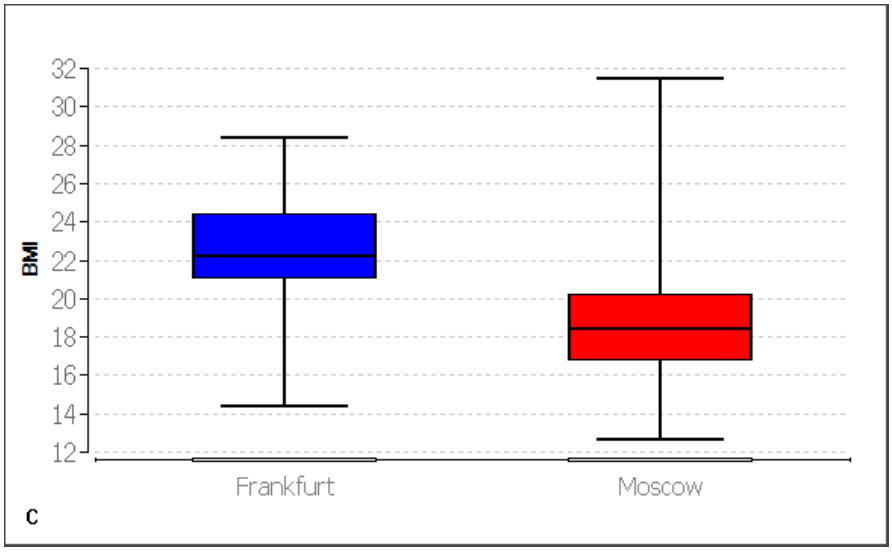
Patients aged 16 to 18 years:



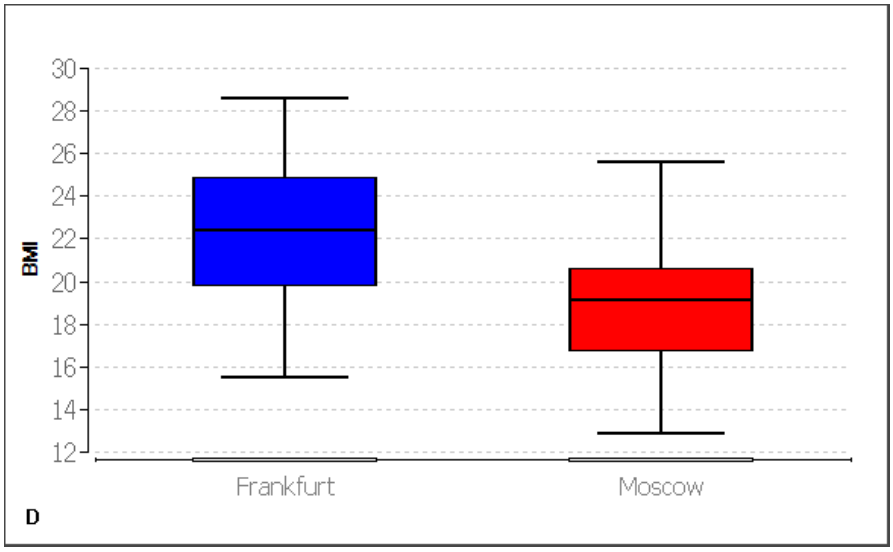
Patients aged 19 to 22 years:



Patients aged 23 to 29 years:



Patients aged 30 to 35 years:



Patients older than 35 years:

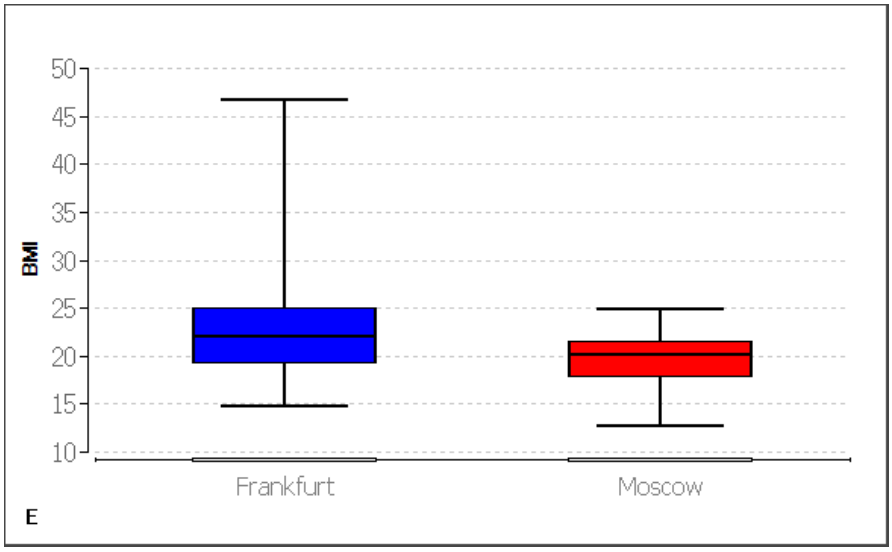


Fig. 5: *Box plots representing BMI comparison of patients for 2015 with median, first quartile and third quartile.*

A) *Patients aged 16 to 18 years (Average BMI: Frankfurt (n=12): 19.95; Moscow (n=25): 17.90 – Median BMI: Frankfurt (n=12): 19.99; Moscow (n=25): 17.58).*

B) *Patients aged 19 to 22 years (Average BMI: Frankfurt (n=19): 20.87; Moscow (n=76): 18.75 – Median BMI: Frankfurt (n=19): 20.56; Moscow (n=76): 18.75).*

C) *Patients aged 23 to 29 years (Average BMI: Frankfurt (n=25): 22.59; Moscow (n=139): 18.66 – Median BMI: Frankfurt (n=25): 22.22; Moscow (n=139): 18.38).*

D) *Patients aged 30 to 35 years (Average BMI: Frankfurt (n=29): 22.27; Moscow (n=44): 18.97 – Median BMI: Frankfurt (n=29): 22.41; Moscow (n=44): 19.14).*

E) *Patients older than 35 years (Average BMI: Frankfurt (n=56): 23.03; Moscow (n=17): 19.93 – Median BMI: Frankfurt (n=56): 22.03; Moscow (n=17): 20.08).*

In 2015 Moscow CF patients stratified by age groups had statistically significant lower BMI than Frankfurt CF patients in all age groups (age 16-18: p=0.003; age

19-22: p=0.004; age 23-29: p<0.001; age 30-35: p<0.001; age 36-66: p=0.024)[108-111].

3.5. Comparison of FEV1 in matched samples in 2015

To compare FEV1 in both centers a program run with R-Studio[102] allowed isolation of samples of matched pairs by height (before matching p=0.028, after matching p=0.876), age (before matching p<0.001, after matching p=0.484) and sex category (before matching p=0.088, after matching p=0.258) for 2015. Both samples included 100 patients (first sample with 100 Frankfurt patients and second sample with 100 Moscow patients) and were comparable after matching. Statistical analysis showed FEV1 was significantly lower for Moscow CF patients (p<0.001) than for Frankfurt CF patients in 2015.

FEV1	Average	Median	SD	Maximum	Minimum
Frankfurt	2497.90	2420.00	1143.19	5410.00	750.00
Moscow	1908.70	1615.00	1044.80	5220.00	520.00

FEV1	Range	1st quartile	3rd quartile
Frankfurt	4660.00	1537.50	3325.00
Moscow	4700.00	1222.50	2487.50

Table 4: *Biometrical statistical analysis of FEV1 in 2015 for both samples (n=100 CF-patients in Frankfurt and n=100 CF-patients in Moscow). Average, median, SD, maximum, minimum, range, first quartile and third quartile are higher in Frankfurt than in Moscow.*

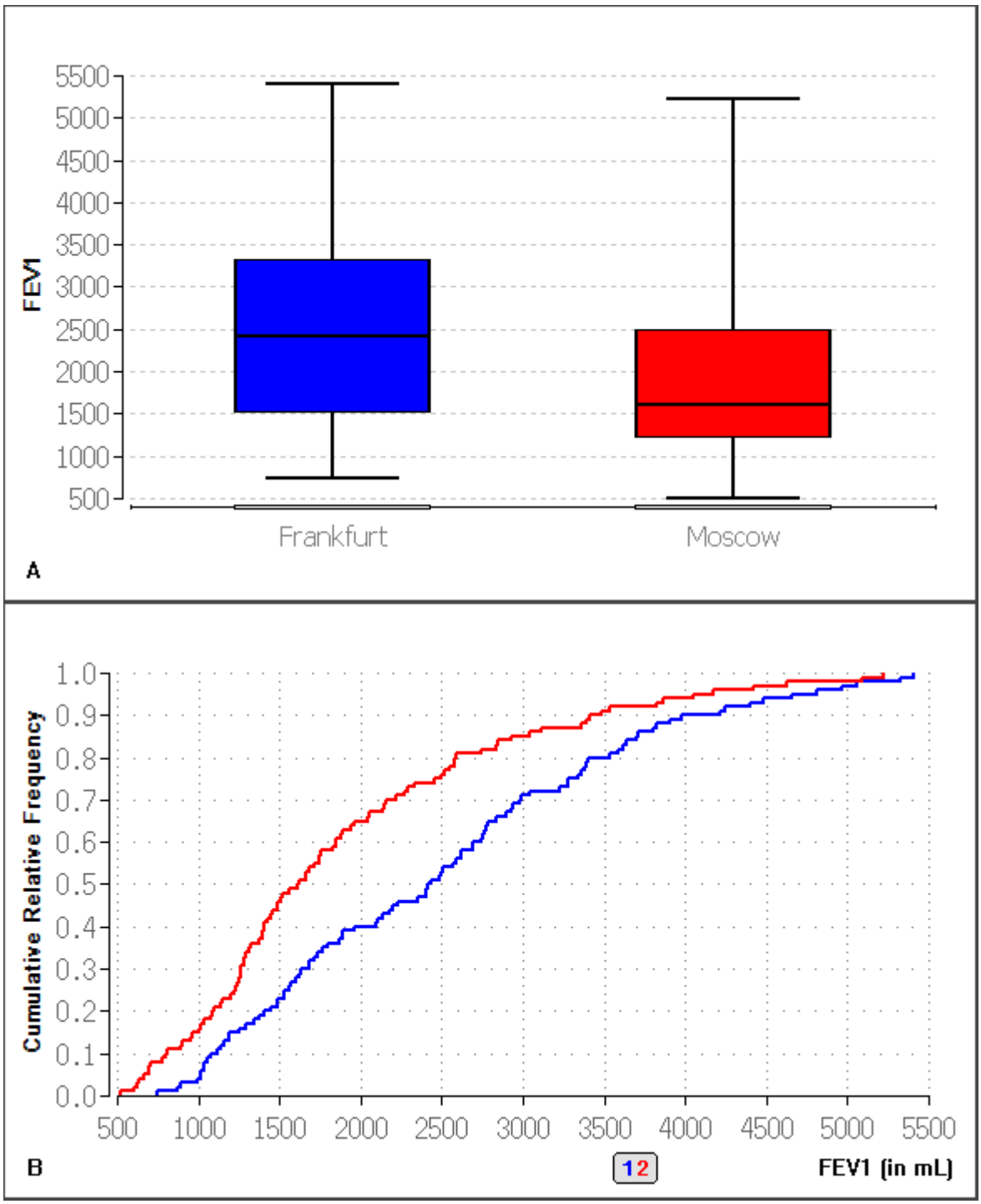


Fig. 6: ***A)*** *Box plot representing FEV1 comparison of both matched samples for 2015 with median, first quartile and third quartile.*

B) *Empirical distribution function of FEV1 in both samples (blue=Frankfurt, red=Moscow) for 2015.*

3.6. BMI comparison with normal population

Age group (in years)	Mean BMI
18-20	22.7
20-25	23.5
25-30	24.5
30-35	25.1
35-40	25.5
40-45	26.0
45-50	26.1
50-55	26.4
55-60	26.7
60-65	27.0
65-70	27.3
70-75	26.9
>75	24.5

Table 5: *Data from the German federal office of statistics[104] show mean BMI in Germany for different age categories in 2017. For 18 to 20 year old people the mean BMI was 22.7, in the age group 20 to 25 year BMI was 23.5, while 25 to 30 year old people had a BMI of 24.5. For 30 to 35 year old people it´s 25.1. For 35 to 40 year old people it´s 25.5. For 40 to 45 year old people it´s 26.0. For 45 to 50 year old people it´s 26.1. For 50 to 55 year old people it´s 26.4. For 55 to 60 year old people it´s 26.7 For 60 to 65 year old people it´s 27.0. For 65 to 70 year old people it´s 27.3. For 70 to 75 year old people it´s 26.9. For people elder than 75 years it´s 24.5. This leads to a mean BMI of 26.0 for German population.*

Russian data[105-107] are not equally detailed. In 2014 mean BMI in the Russian population was 26.5. In the same year mean BMI was 26.3 in Germany, this might mean that the Russian population has a higher mean BMI than the German population. Consequently gap in BMI in our both CF-populations (referred to 3.4.) cannot be explained by epidemiological data of the normal population.

3.7. CF guideline comparison between Frankfurt and Moscow

Field	Question	Guideline[43]	Moscow	Frankfurt
Hygiene and prevention	1. How often do CF patients have to present themselves for CF follow up?	Presentation every 1-3 months, ideally every month. In newly diagnosed children or patients with severe illness, control intervals <1 month. With mild CF presentation every 3-6 months.	Presentation monthly, but in some cases only once every 6 months.	CF patients are routinely seen every 3 months for a check-up at the CHCF center (Christiane Herzog CF center), more often if necessary. A current referral slip is required for treatment at the CHCF center: • In adults by the family doctor; • For children from the specialist for pediatric and adolescent medicine. Re-appointments are usually arranged with the patient and with children with the parents at the current appointment.

Field	Question	Guideline[43]	Moscow	Frankfurt
				Appointments can also be done by phone or email.
Hygiene and prevention	2. Where must control be carried out?	In a designated clinic / center / department of a hospital.	CF center of the Institute of Microbiology.	In the CHCF of the University Hospital Frankfurt.
Hygiene and prevention	3. Who carries out control?	1 CF doctor and 1 CF nurse (other department employees must also be available if required).	Pneumologist, cystic fibrosis specialist.	Specialized hygiene officers*.
Hygiene and prevention	4. What does the visit / control include?	Clinical examination, weight measurement, oximetry, age-related lung function tests, decrease in sputum or cough cultures, size measurement for children and head circumference measurement for very young	Spirometry (sitting with a 15-minute break), auscultation, lung function test.	> Every 3 months (" routine check ** 1 ") are carried out: • Physical examination; • Further investigations: →In adults: • Weighing (weight); • Microbiology (if sputum cannot be coughed up then

Field	Question	Guideline[43]	Moscow	Frankfurt
		children.		in; • Exceptions! Throat swab, nasal swab in Pseudomonas-free patients); • "Small" blood sampling (including blood count and inflammation parameter CRP); • "Small" lung function (spirometry). →In children: • Weighing (weight) and body length; • Microbiology; • Blood sampling (symptom-oriented outside the annual check-up dates); • Spirometry.
Hygiene and prevention	5. How is the control carried out in patients with B.	Control on different days or in separate rooms / locations / sta-	As in other cases, but with anti-epidemic	Resistant and / or "special" germs (e.g. Burkholderia complex, MRSA,

Field	Question	Guideline[43]	Moscow	Frankfurt
	cepacia complex, MRSA or P. aeruginosa (Place / time especially with several affected patients)?	tions.	measures.	non-tuberculous mycobacteria of the Abscessus type, multiresistantly defined germs such as 4MRGN): • A spatial germ separation is carried out in the CF center; • Access to CF ambulance via entrance 18 (see access to CF ambulance for P. aeruginosa patients via entrance 18A); • The staff also wear a face mask, a protective coat and protective gloves, when they have contact with patients.
Hygiene and prevention	6. Accessibility of the CF center?	Patients can call the CF Center 24 hours a day	Accessibility in Moscow from 5 minutes to 1	Patients can call the CF Center for 24 hours a day

Field	Question	Guideline[43]	Moscow	Frankfurt
		for a medical presentation. Emergency visits can happen through direct contact. It is also recommended that a CF specialist nurse is available to answer patient questions at certain times.	hour. From Vladivostok: 12 hours flight time.	for medical consultation or emergencies At certain times, a CF-specialized doctor or a CF-specialized nurse is available for patient inquiries → Not carried out yet in Frankfurt, but soon (currently a bronchoscopy doctor from the CF team is always available - he can call in the "right" CF doctor)*.
Hygiene and prevention	7. Is there an infection / hygiene team?	Infection and hygiene team for infection control must be available.	Infection and hygiene specialists available.	Infection and hygiene team for infection control available.
Hygiene and prevention	8. Bed distribution?	Beds must be in single rooms to prevent cross-infection or transmission of germs between	20 single rooms available at the same time with a waiting time of 1 to 7	Beds are organized in single rooms, own toilet and bathroom available per bed/ room*.

Field	Question	Guideline[43]	Moscow	Frankfurt
		patients. It is also recommended to have an own toilet and bathroom per bed/ room.	days. Own toilet and shower are available.	
Hygiene and prevention	9. Hygiene and disinfectant presence?	Hand washing facilities (e.g. wash basins) in every patient cabin available, as well as alcohol-based disinfectants and detergents available.	Detergents and disinfectants are available (washbasins and disinfectants with alcohol).	Hand washing facilities (e.g. wash basins) in every patient cabin, as well as alcohol-based disinfectants and detergents available*.
Hygiene and prevention	10. Separation from B. cepacia complex or MRSA patients?	Must be handled at different stations to prevent transmission. B. cepacia patients: • Must be treated in separate rooms, also to avoid transmission;	Patients are separated.	Patients are treated at different wards (but actually in the same ward due to lack of space) to prevent transmission. B. cepacia patients: • Treated in sepa-

Field	Question	Guideline[43]	Moscow	Frankfurt
		• Not meeting of patients in hospitals (transmission prevention); • Social contacts outside the hospital with B. cepacia must be avoided (transmission prevention).		rate rooms, also to avoid transfers; • Cannot meet each other in the hospital (transmission prevention); • Have to avoid social contacts outside the hospital with B. cepacia-infected patients (transmission prevention).
Hygiene and prevention	11. Assessment of hyperglycaemia and cross-night oxygen saturation when ingested?	With each admission, hyperglycaemia and cross-night oxygen saturation must be assessed during the event of infection exacerbations.	Hyperglycaemia is assessed with each new admission.	Assessment of hyperglycaemia and cross-night oxygen saturation in the case of infectious exacerbations performed with each admission*.
Hygiene and prevention	12. Sputum analysis and spirometry?	Perform sputum analysis and spirometry once	Performed sputum analysis and	Sputum analysis and spirometry performed once a

Field	Question	Guideline[43]	Moscow	Frankfurt
		a week.	spirometry once a week.	week*.
Hygiene and prevention	13. Annual assessment?	An annual assessment must be carried out to enable the success of the therapy.	Annual assessment is carried out.	Annual assessment is carried out.
Therapy indication	1. Patient consultation / review?	Discussion of the inpatient care patients and i.v. antibiotic outpatient care (currently at home) patients at least once a week in a multidisciplinary consultation with all members of the CF team, as well as the doctors and nurses on the ward.	There are nurses on the ward.	Discussion of the inpatient care and i.v. antibiotic outpatient care patients at least once a week in a multidisciplinary consultation with all members of the CF team, as well as the doctors and nurses on ward*.
Therapy indication	2. Antibiotic treatment after pulmonary exacerbation?	Depending on the clinical course, we recommend primary intravenous	Primarily i.v. therapy, followed by inhalation therapy.	Depending on the clinical course: primarily intravenous therapy in patients with

Field	Question	Guideline[43]	Moscow	Frankfurt
		therapy in patients with pulmonary exacerbation combined with subsequent inhalation therapy with colistin / ciprofloxacin p.o. or tobramycin.		pulmonary exacerbation combined with a subsequent inhalation therapy with colistin / ciprofloxacin p.o. or tobramycin. This is patient-specific That may apply, but does not have to*.
Therapy indication	3. What therapy is required if the attempt of eradication wasn´t successful?	If a first eradication cycle is unsuccessful, the following therapy alternatives should be considered: • An i.v. colistin therapy over 2 weeks or therapy with inhalated colistin plus high dose oral ciprofloxacin (3x 2 million IU) • Later: oral ciprofloxacin for	I.v. therapy for 2-3 weeks or inhalation therapy in combination with oral therapy. If these approaches are unsuccessful too: switch to other antibiotic combinations	If an initial eradication cycle is unsuccessful: • An i.v. colistin therapy over 2 weeks or high dose inhalated colistin plus high dose (3x 2 million IU) oral ciprofloxacin • Later: oral ciprofloxacin for 3 months or inhaled tobramycin in a dose of 2x 300 mg over 4 weeks.

Field	Question	Guideline[43]	Moscow	Frankfurt
		3 months or inhaled tobramycin in a dose of 2x 300 mg over 4 weeks. If inhalation is not possible, the i.v. therapy should be repeated over 14 days and possibly other combinations can be used (expert opinion).		If inhalation is not possible: • I.v. therapy repeated over 14 days and possibly others antibiotic combinations. → In Frankfurt, treatment is based on the newest guideline*.

Field	Question	Guideline[43]	Moscow	Frankfurt
Therapy	1. Start of treatment and treatment conditions?	Clinical or domestic i.v. antibiotic therapy can be organized in 24-48h. Initial dose (starting dose) of antibiotic i.v. therapy supervised/ monitored by medical staff.	Clinical or home antibiotic therapy.	Clinical or domestic i.v. antibiotic therapy organized in 24-48h. Initial dose (starting dose) of antibiotic i.v. therapy supervised/ monitored by medical staff*.
Therapy	2. Availability of physiotherapists, dietitians and social workers?	Monitoring and therapy by physiotherapists, dietitians, social workers and other in therapy involved staff must be available	Supervision by various medical specialists.	Monitoring and therapy by physiotherapists, dietitians, social workers and other in therapy involved staff available.*

Field	Question	Guideline[43]	Moscow	Frankfurt
Therapy	3. Physiotherapy and sputum mobilization?	Sputum mobilization therapy and physiotherapy should be performed 2 times a day.	It is depending on the state of patients' health: physiotherapy, sport.	Depending on the state of patients' health: sputum mobilization therapy and physiotherapy are carried out twice a day for patients with poor health, and sport is recommended for "healthier" patients*.
Therapy	4. Equipment for checking physical activities and therapy monitoring?	Therapy monitoring for physiotherapy, such as pulse oximetry and oxygen inhalers, must be available.	Pulse oximetry is available.	Therapy monitoring for physiotherapy, such as pulse oximetry and inhalation devices are available*.
Therapy	5. Logging of antibiotic therapy?	Protocols about: • Administration and dosage of the antibiotics must be available (including measurements of the Blood serum	Protocols about: • Condition, dosage of antibiotics, blood sugar etc. .	Protocols about: • Administration and dosage of the antibiotics are done (including measurements of the Blood serum concentration of

Field	Question	Guideline[43]	Moscow	Frankfurt
		concentration of antibiotics).		antibiotics)*.
Therapy	6. Communication between CF center and "home clinic"?	Satellite CF center (used especially if travel distance to the actual CF center is too wide for patients affected to be visited regularly) must permit to have a look after at least 20 CF patients and must include specialized CF dietitians, CF physiotherapists and CF nurses.	Pneumologists in conjunction with cystic fibrosis specialists are available in satellite CF centers.	Frankfurt has no satellite outpatient clinics and is certified as a "single center"*.
Therapy	7. Standards in the satellite CF center?	An equivalent standard to the main CF center must be available.	It is depending on intellectual reserve, wishes and financial regional means.	-
Therapy	8. Control of patients in the satellite CF center?	The team at the main CF center has to see patients 1-2 times	Presentation of patients at the main CF center in Mos-	-

Field	Question	Guideline[43]	Moscow	Frankfurt
		a year (either by introducing the patient to the main CF center or by visits by main CF center staff in the satellite CF center).	cow 1-2 times a year.	
Therapy	9. When does the transition of CF child care to CF care for adult patients occurs?	Usually it occurs between 16 and 18 years, depending on health status and social maturity.	There are 4 CF centers for children in Moscow. The children are observed up to 18 years and then supported in adult CF centers.	-
Therapy	10. Is there any cooperation between pediatric and adult CF centers?	Close cooperation is mandatory between pediatric and adult CF centers to enable the development, update and revision of therapy guidelines.	There is a very close cooperation between both types of CF centers.	-

Field	Question	Guideline[43]	Moscow	Frankfurt
Therapy	11. Which antibiotic resistance are tested?	First choice: piperacillin, ceftazidime, meropenem, tobramycin, ciprofloxacin, colistin /// Second choice: piperacillin-tazobactam, cefepim, gentamicin, amikacin, aztreonam, fosfomycin, doripenem	Resistance is always tested for all of them.	-
Therapy	12. Are there antibiotic treatment options for patients with Pseudomonas in the lower airways?	Recommendation: • Early eradication with inhaled tobramycin for 4 weeks or oral ciprofloxacin combined with inhaled colistin for 3 weeks; • If inhalation is not possible, intravenous combination	Early eradication therapy: • Inhalation first. If this remains unsuccessful i.v. therapy or inhalative and i.v. therapy in combination should be tested.	Early eradication with: • Inhaled tobramycin for 4 weeks or oral ciprofloxacin combined with inhaled colistin for 3 weeks. • If inhalation isn´t possible, intravenous combination therapy has to be carried out.

Field	Question	Guideline[43]	Moscow	Frankfurt
		therapy should be considered.		
Therapy	13. Is there any adjustment of antibiotic therapy according to patients' age?	Reference N ° 1.	Therapy scheme according to reference N ° 1.	Therapy scheme according to reference N ° 1*.
Therapy	14. Should patients inhale with hypertonic saline or with Dornase alfa?	It is recommended that regardless of PA colonization, an individual decision whether inhalation of Dornase alfa or hypertonic saline has to be done or not.	Inhalation of Dornase alfa or hypertonic saline is done in individual cases regardless of Pseudomonas aeruginosa infection*.	Inhalation of Dornase alfa or inhalation with hypertonic saline done in individual cases regardless of Pseudomonas aeruginosa infection*.

Field	Question	Guideline[43]	Moscow	Frankfurt
Therapy	15. Should physiotherapy and sport be started after initial PA presence?	It is recommended that CF patients start with physiotherapy and (depending on age) sport regardless of PA colonization, as early as possible after diagnosis.	Physiotherapy and sport must be started as early as possible.	Physiotherapy (or/and sport - depending on age) is started as early as possible after diagnosis regardless of Pseudomonas aeruginosa colonization*.

** Information from Dr. Smaczny*

*** 1: Once a year, a so-called "annual check-up" is carried out instead of the "routine check"*

Reference N°1: As far as possible, inhalation therapy is strived for young children. Children under 3 years of age usually inhale through a mask. If inhalation is not possible, intravenous antibiotic therapy can be used. Tobramycin inhalation is carried out with 2x 80 mg to 2x 300 mg. The tobramycin inhalation takes place in patients older than 6 years with tobramycin 2x 300 mg in on/ off mode for 28 days each. In Germany, inhalation is also common with tobramycin carried out with 2x 80 mg, with a continuous inhalation without off mode. Therapy with ciprofloxacin orally can start with 40 mg / kg per day in the first month of life. In some centers, colistin inhalation is increased according to a step-by-step scheme or with higher dose after repeated pathogen detection: It starts with 2x 1 million for 3 weeks at first detection. If the pathogen is detected again, it is increased to 3x 2 million, also over 3 weeks. With each additional pathogen detection, the same dosage and extension of the inhalation for 3 months is indicated. If the eradication attempt with inhaled and oral antibiotics is unsuccessful or if there is a pulmonary exacerbation

at the initial detection, an intravenous antibiotic therapy usually in a combination of aminopenicillins with a third generation cephalosporins should be administrated.[112]

Table 6: Application of *CF*[43] *guidelines in Frankfurt and Moscow. Guidelines about* ***outpatient care*** *in* ***blue****,* ***inpatient care*** *in* ***pink*** *and* ***lower respiratory tract infection*** *in* ***yellow****, empty fields in* ***gray****.*

This table is based on internationally proposed guidelines[43]. It shows how the international guidelines are implemented in both centers and what resources are available. The standardized operational procedures (SOPs) in Frankfurt and Moscow were reported according to the local center directives[112] and interviews with local experts. Many differences can be noticed and are discussed below.

4.Discussion

Design of the study

Different studies have shown that prognosis in CF is related to Body-Mass-Index (BMI)[89], Forced Expiratory Volume in 1 second (FEV1)[90], and need of intravenous antibiotic therapy [43]. They have significant impact on survival and the quality of life of CF patients [91] and are widespread used for CF studies. This is why we decided to pick up these three parameters for our study and to compare their values between both CF centers.

At first we had to analyze epidemiological available data of normal population to see if both are reasonably comparable. Latest data from the German federal office of statistics[104] shows a mean BMI of 26.0 for German population in 2017. Russian data[105-107] are not equally detailed and latest data was published in 2014. Mean BMI in the Russian population was 26.5. In the same year mean BMI was 26.3 in Germany, this might mean that the Russian population has a higher mean BMI than the German population, however both populations can be considered comparable. Consequently a possible gap in BMI in both CF-populations (referred to 3.4.) cannot be explained by epidemiological data of the normal population.

Available data from CF patients according to European Cystic Fibrosis Patient Registry (ECFSPR) annual report in 2017 show country gaps for CF parameters. A comparison of BMI in 2017[3] between Germany and the Russian Federation in the table below shows a difference for patients categorized in age and sex groups. Average and mean values are closer to normal in Germany for adults (men and women).

	Mean BMI	Median BMI (50% of the patients are below this BMI)
Germany (Patients aged 18 years or older)	**21.50**	**21.10**
Russian Federation (Patients aged 18 years or older)	**19.60**	**19.10**
Germany (Male patients aged 18 years or older)	**21.90**	**21.60**
Russian Federation (Male patients aged 18 years or older)	**20.00**	**19.40**
Germany (Female patients aged 18 years or older)	**21.00**	**20.50**
Russian Federation (Female patients aged 18 years or older)	**19.10**	**18.70**

Table 7: *BMI: descriptive statistics[3], comparison by country, age and sex groups, 2017.*

In summary, according to ECFSPR annual report of 2017 the BMI of Germany and the Russian Federation are different. German patients' BMI is higher than that of Russian patients, this is true for patients older than 18 years, regardless of whether

female or male. Furthermore BMI[89] is a significant surrogate marker for CF lifetime prognosis, what increases the importance of this value.

Another important CF marker is the FEV1%. It is a significant surrogate marker[90] for CF overall prognosis of survival with a high grade importance. A comparison of FEV1% between Germany and the Russian Federation in the table below shows a difference for patients categorized in age groups. Average and mean values seem higher in Germany for children and for adults, a statistical analysis of the published data could not be done.

	Average FEV1% (mean)	**Median (50% of patients have a FEV1 below this value)**
Germany (Patients aged 6-17 years who have never had a lung transplant.)	**90.1**	**92.5**
Russian Federation (Patients aged 6-17 years who have never had a lung transplant.)	**82.9**	**83.9**
Germany (Patients aged 18 years or older who have never had a lung transplant.)	**65.4**	**65.6**
Russian Federation (Patients aged 18 years or older who have never had a lung transplant.)	**57.5**	**55.3**

Table 8: *FEV1%: descriptive statistics[3], comparison by country and age groups, 2017.*

The values grouped in the two figures below show the FEV1% in different age groups for both countries in 2017. The dot shows the median. The first quartile and third quartile are represented by the whiskers. The country quartiles are blue; the pooled quartiles calculated for the 2017 ECFSPR annual report[3] regrouping the whole ECFS countries are in red and represent the pooled quartiles on all other countries (i.e. excluding the country compared).

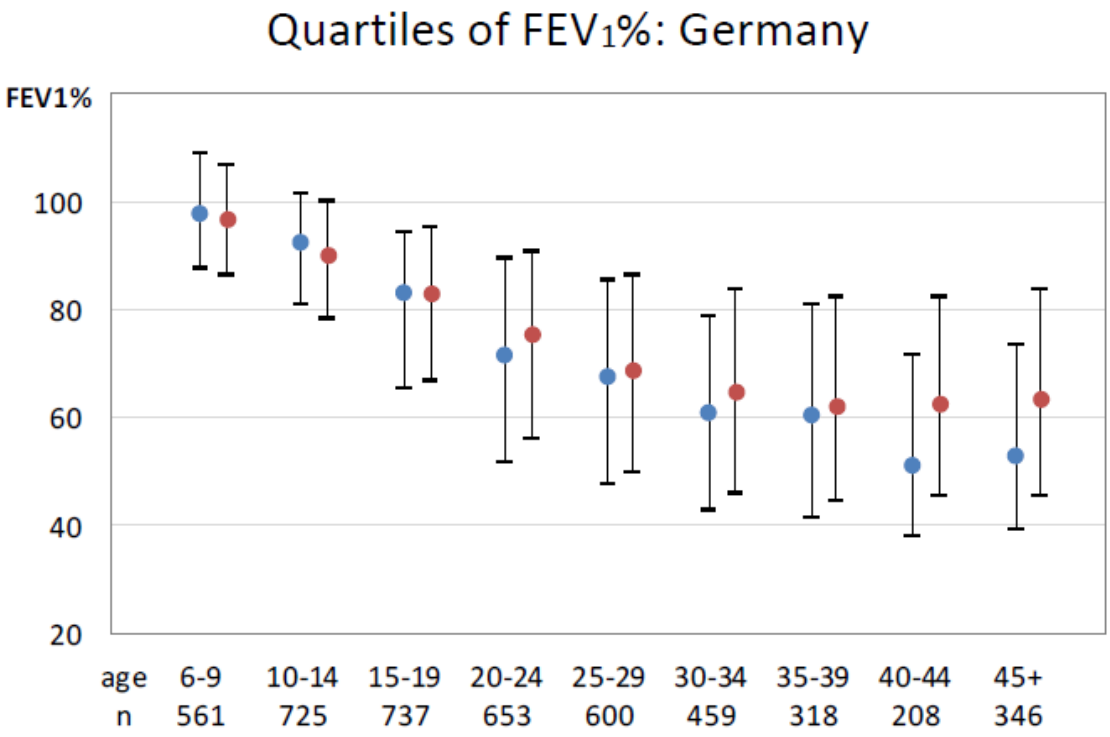


Fig. 7: *The values show the FEV1% in different age groups for Germany and the other ECFS countries[3]. The quartiles of Germany are blue; the pooled quartiles regrouping the whole ECFS countries except the data from Germany are in red.*

From 6 to 39 years Germany´s data is comparable with the pooled data. For patients 40 years and older Germany´s FEV1% values seem to be lower than the FEV1% values of the other ECFS states.

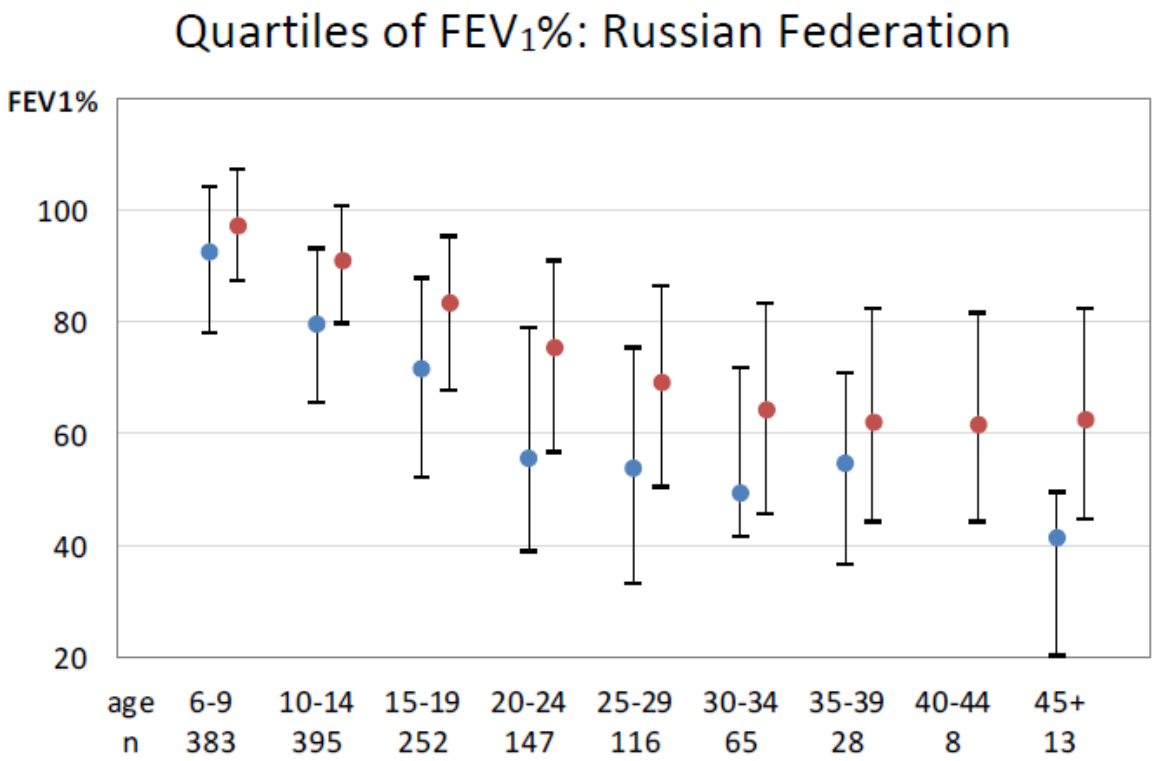


Fig. 8: *The values show the FEV1% in different age groups for the Russian Federation and the other ECFS countries[3]. The quartiles of the Russian Federation are blue; the pooled quartiles regrouping the whole ECFS countries except the data from patients from the Russian Federation are in red.*

In all age categories Russian FEV1% values seem to be lower than the FEV1% values of the other ECFS countries. For the age category 40 to 44 years data is missing and no comparison could be established.

In summary, according to ECFSPR annual report of 2017 the FEV1% of Germany and the Russian Federation are different. German data seem to resemble the pooled data very closely, while the Russian data seem to be lower than pooled data and German data. This is the reason why we expected differences between both centers we wanted to analyze.

Finally, a third parameter was collected: the presence of chronic Pseudomonas aeruginosa in CF patients. This parameter has a direct influence on CF patient

survival and is very important because it is linked to the necessity of intravenous antibiotic therapy, which is a surrogate parameter. Prognosis in CF depends on the need of intravenous antibiotic therapy as a result of a severe pulmonal exacerbation [61] or a chronic P. aeruginosa infection [96]. In the table below the chronic P. aeruginosa prevalence was determined in adults and children for the year 2017.

	Missing	Positive (Yes)	Negative (No)
Number of chronic Pseudomonas aeruginosa infection observed in **Germany**	278	3736	2105
Prevalence of chronic Pseudomonas aeruginosa infection observed in **Germany** (in %)	4.54	61.06	34.40
Number of chronic Pseudomonas aeruginosa infection observed in the **Russian Federation**	96	2020	964
Prevalence of chronic Pseudomonas aeruginosa infection observed in the **Russian Federation** (in %)	3.12	65.58	31.30

Number of chronic Pseudomonas aeruginosa infection in children seen in **Germany**	70	2231	260
Prevalence of chronic Pseudomonas aeruginosa infection in children seen in **Germany** (in %)	2.73	87.11	10.15
Number of chronic Pseudomonas aeruginosa infection in children seen in the **Russian Federation**	49	1715	612
Prevalence of chronic Pseudomonas aeruginosa infection in children seen in the **Russian Federation** (in %)	2.06	72.18	25.76
Number of chronic Pseudomonas aeruginosa infection in adults seen in **Germany**	208	1505	1845
Prevalence of chronic Pseudomonas aeruginosa infection in adults seen in **Germany** (in %)	5.85	42.30	51.85

Number of chronic Pseudomonas aeruginosa infection in adults seen in the **Russian Federation**	47	305	352
Prevalence of chronic Pseudomonas aeruginosa infection in adults seen in the **Russian Federation** (in %)	6.68	43.32	50.00

Table 9: *Prevalence of chronic bacterial infection in all patients seen in 2017[3], by country.*

To get a better overview of these numbers the prevalence is represented in histograms below.

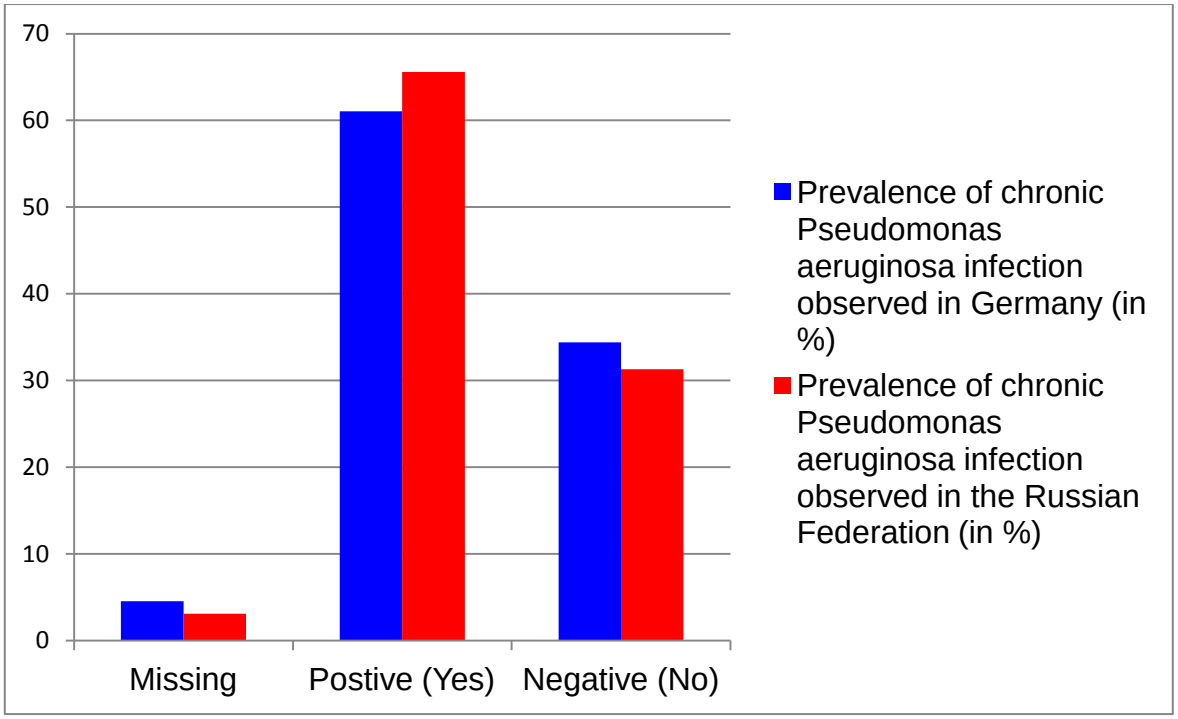


Fig. 9: *Prevalence of chronic Pseudomonas aeruginosa infection observed in Germany and the Russian Federation (in %).*

According to ECFSPR annual report of 2017[3], we could observe the prevalence of chronic P. aeruginosa infection in both countries is quite similar. The rate of missing values is below 5 percent in both countries. The rate of presence of P.aeruginosa in all patients is above 60 percent in both countries and seems to be a little higher in the Russian Federation (65.58%), compared to Germany (61.06%).

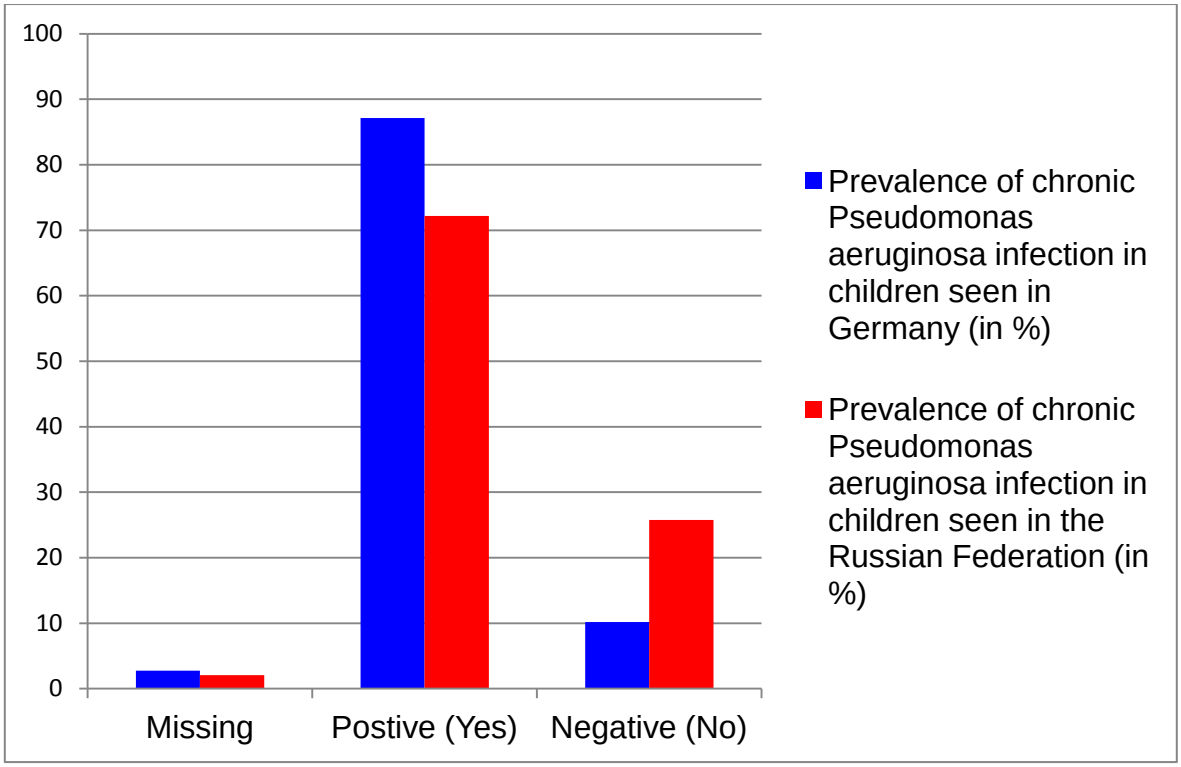


Fig. 10: *Prevalence of chronic Pseudomonas aeruginosa infection observed in children in Germany and the Russian Federation (in %).*

According to ECFSPR annual report of 2017[3], we could observe the prevalence of chronic P. aeruginosa infection in children (patients under 18 years old) in both countries is different. The rate of missing values is below 3 percent in both countries. The rate of presence of Pseudomonas aeruginosa in patients is above 80 percent in Germany (87.11%) and below 75% in the Russian Federation (72.18%).

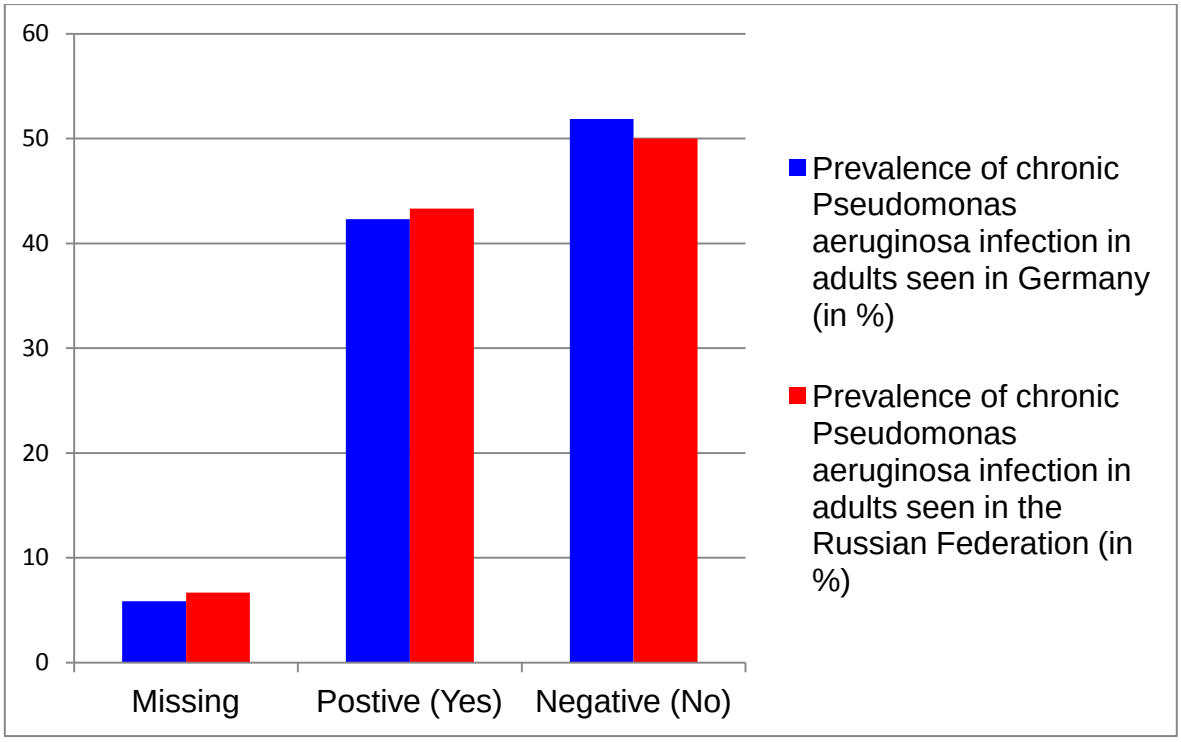


Fig. 11: *Prevalence of chronic Pseudomonas aeruginosa infection observed in adults in Germany and the Russian Federation (in %).*

For patients older than 18 years,the ECFSPR annual report of 2017 shows a similar prevalence of chronic P. aeruginosa infection in both countries with a missing value rate below 7 percent. The rate of presence of P.aeruginosa in patients is below 50 percent in both countries, with 42.30% in Germany and with 43.32% in the Russian Federation.

In both countries, the highest rate of chronic P. aeruginosa infection in CF patients is found in patients below the age of 18. This could be related to an earlier time of death of patients infected with Pseudomonas aeruginosa and has to be proven in further studies. Nevertheless, Russian children with CF have proportionately less chronic P. aeruginosa infection than German children. German adults with CF, however, have a little less chronic P. aeruginosa infection than Russian adults. Due to age distribution effects (younger CF patient population in Russia[3]) Russian CF patients have a higher prevalence of chronic P. aeruginosa infections than German CF patients.

Comparison of the data of this study with data available in literature

The data quality of our study should be discussed. First of all, it should be mentioned that data were not available from every patient every year. This is why the significance of the data should be nuanced. As an example, in 2015 for the entire cohort, only 486 out of 587 entries (82.79%) were found for the BMI, only 440 out of 587 (74.96%) entries were found for FEV1 and only 492 out of 587 (83.82%) entries were found for intravenous antibiotic therapy. This shows that a significant amount of data is missing and that the quality of the data is negatively affected.

Moreover, the data was collected on one hand by doctors and clinic employees, which makes human bias in the data collection possible. On the other hand, this clinically collected data is entered manually into the computer system, which makes further errors possible and can explain missing data. Single entries in the clinic system were incomplete and not optimally documented. This was particularly the case for intravenous antibiotic therapy. The accuracy of the data, in particular for this parameter, can therefore be questioned.

Another problem is that the devices, with which the values for the BMI and the FEV1 were collected, was not documented. The balance systems used were neither described nor entered in the survey. Furthermore, it was not written down whether the FEV1 values were determined using spirometry or bodyplethysmography. Local experts said that it was mostly collected via spirometry. Unfortunately, this is not documented for every individual case. Calibration of devices is important for data precision. According to local experts, clinical rules and guidelines, this was the case for our study.

Deviations due to anomalies were also found in the patient's follow-up data. These have also affected the quality of the data and thus reduced the representativeness of the data.

In our study we could observe the Russian cohort is significantly younger than the German cohort. Average[108] age was 33.57 for Frankfurt, 25.59 for Moscow and for

the total cohort 28.14. According to ECFSPR in 2017 mean average age was 22.4[3] years in Germany and 12.4[3] years in Russian Federation what confirms our results.

In Moscow 217 (50.70%) male patients and 211 (49.30%) female patients were counted, while in Frankfurt 92 (57.86%) male patients and 67 (42.14%) female patients were registered. According to ECFSPR in 2017 in Germany around 52% were male patients and 48% were female.[3] In Russian Federation the percentage was similar with about 51% male patients and 49% female patients[3]. These results were comparable with our study for Moscow. In Frankfurt the relative amount of male patients was higher than the German average. The observed gender gap could have influenced our results.

Because of the data problems described previously, BMI and FEV1 aren't statistically significant. We had to clean up the individual parameters from disruptive data and perform a cross-sectional analysis to obtain significant data. As a result of that we analyzed BMI between both centers for the year 2015. Moscow CF patients stratified by age groups had statistically significant lower BMI than Frankfurt CF patients in all age groups according to 3.4. (age 16-18: $p=0.003$; age 19-22: $p=0.004$; age 23-29: $p<0.001$; age 30-35: $p<0.001$; age 36-66: $p=0.024$)[108-111]. According to ECFSPR in 2017 we found a smaller BMI gap with a BMI of 21.50 for Germany and a BMI of 21.10 for the Russian Federation[3].

To analyze FEV1 values we had to match some parameters with influence on it, including height, age and sex category. This was the result of a lack of values not allowing us to use FEV1%. Statistical analysis showed FEV1 was significantly lower for Moscow CF patients ($p<0.001$) than for Frankfurt CF patients in 2015 for matched pairs by height (before matching $p=0.028$, after matching $p=0.876$), age (before matching $p<0.001$, after matching $p=0.484$) and sex category (before matching $p=0.088$, after matching $p=0.258$). According to ECFSPR annual report in 2017 German data seems to resemble the pooled data for all ECFS countries very

closely[3], while the Russian data seem to be lower than pooled data and German data[3]. This is in line with our FEV1 results in Frankfurt and Moscow.

Intravenous antibiotic therapies are usually done to treat pulmonary exacerbation (often due to chronic P. aeruginosa infection) in CF patients and frequency correlates with number of exacerbations. A clean-up of data didn´t help to obtain satisfying significant values concerning the intravenous antibiotic therapies, because of inaccurate documentation and unsatisfactory data situation. Intravenous antibiotic therapies in Moscow were carried out more frequently than in Frankfurt in 2015, however, these differences were not statistically significant over a longer period of observation($p>0,1$). According to ECFSPR annual report of 2017[3], we could observe the prevalence of chronic P. aeruginosa infection in both countries is quite similar. The rate of presence of P.aeruginosa in all patients is above 60 percent in both countries and seems to be a little higher in the Russian Federation (65.58%), compared to Germany (61.06%). This confirms our study results indicating higher exacerbation rates in Moscow. Due to age distribution effects (younger CF patient population in Russia[3]) Russian CF patients have a little bit higher prevalence of chronic P. aeruginosa infections than German CF patients.

Possible explanation for the observed differences

According to our expectations, BMI, FEV1 and chronic P. aeruginosa infections show a gap between both countries and this gap was shown partly by our both centers results too. Frankfurt is closer to normal values for BMI and FEV1 than Moscow. Only for the necessity of intravenous antibiotic therapy the gap wasn´t statistically significant, what can possibly be explained by a lack of documentation in both centers and not always regular clinical examination. Patients are not forced to appear regularly and often just come when the CF exacerbation or the illness is high grade. The missing gap can also be explained by the different amount of testing in both countries. No exact data about P. aeruginosa testing has been published in both countries. The ECFSPR reports however around 3000 P. aeruginosa tests in 2017 in Russia[3], meanwhile around 6000 P. aeruginosa tests in Germany[3].

Finally P. aeruginosa tests are realized twice as much in Germany than in Moscow. Fewer tests can contribute to a smaller number of detected P. aeruginosa cases (this phenomenon was also observed for the coronavirus pandemic in 2019-2020[113,114]). This could partially explain why the gap found in our study between Frankfurt and Moscow is not significant. Another point we have to take into consideration is the demographical difference between both countries. According to 3.6., we can see both countries have no relevant gap for BMI in the healthy population; however, we observed a significant BMI gap for all age categories in CF patients in 2015. To conclude, we can deduce the BMI gap for CF patients in Frankfurt and Moscow cannot be explained by demographical BMI differences.

According to the number of death patient totalized in our study, there were less deaths in Frankfurt than in Moscow. This can be partially explained by new therapies[115-117], a better organisation[112,118] and a medicine that becomes more and more detailed and precise due to the economic possibilities and the research. This means that German patients are in a transition phase, where life expectancy increases. Patients in Russia yet are not in this phase. This may be linked to a possible delay in the use of more modern equipment and therapies, as well as probably lower or unevenly distributed financial means.

We think that quality of care as described above has a significant impact on prognosis in CF. Guidelines try to describe best clinical care. This is why we think it makes sense to look for the adherence to guidelines and especially look for differences in the management of these patients. The differences exposed in the table above in 3.7. may possibly partly explain the differences found for the surrogate parameters before. Guidelines are nevertheless simply indications how the clinical management has to be done and how the health care system has to work. Sometimes there may be deviations of the guidelines due to a lack of financial means, medical equipment, medical resources, to an individual therapy plan and other external factors. Therefore a bias of guidelines can arise. For instance an assessment of microbiological diagnostic procedures for respiratory specimens from CF

patients in German laboratories shows most of laboratories follow guidelines. Some operating anomalies however were observed[119].

Further studies have to be conducted to confirm the different guidelines take part in the gap of CF surrogate parameters and lifetime prognosis. Other causes have still to be considered and are discussed in the conclusions below.

First of all, the economic structures are different between both countries as well as the regional structures of Frankfurt and Moscow. Russia evaluated recently with the independence from the Soviet Union in 1991 and inherited an extensive centralized system[120]. In 1993 a mandatory health insurance (MHI) was introduced to open up an earmarked stream of funding for health care, but faced lots of fiscal constraints[120]. The increase in energy prices on world markets brought welfare, macroeconomic stability, budget surplus and improvements in standards of living for the Russian population, however there is a split between urban and rural populations. Rural populations have worse health and poorer access to health services than urban populations[120]. Russian regions differ significantly in socio-economic, demographic and other parameters[121]. Different approaches to increase the capacity of these regions have to be developed by various type of management to ensure the availability and quality of health care for the population[121]. In Germany, the health system is build up in a different way. The state is organized federally and multiple adapted health care centers were created. This was also reflected in CF management. Since 1995, the German Cystic Fibrosis Quality Assessment project has collected demographic data and outcome parameters, what aims to develop tools for quality management and improve health care[122]. More than 90 CF centers[122] were created in Germany and CF data was collected in “muko.web”[97]. Annual reports are published[97,123] and reveal an ever better coverage of the data year by year. Rapid development in diagnostic and therapeutic options have led to a significant increase in life expectancy[118]. New models of care were created for transition of structures, for instance to reduce the number of adult CF patients treated in pediatric CF institutions. In 2010, around 40% of adult CF patients were treated in pediatric CF institutions[118]. This number was reduced in the past years

and allowed a positive effect on the long-term course of the disease and the prognosis[118]. Different models were tested considering structural local conditions and offering a multidisciplinary treatment approach. Further improvements in the system of cystic fibrosis care are required, exemplarily involvement of patients and their families in quality management[122]. Finally both countries and both centers have different health care and organization strategies due to various parameters and history inheritance. This could also partly explain our results, but has to be confirmed in further studies, where economical, management and organization can be monitored.

5. Conclusions

Data described both CF-populations in Frankfurt and Moscow. At first glance values of BMI, FEV1 and the necessity of intravenous antibiotic therapy were closer to normal in Frankfurt than in Moscow. An evaluation of both CF-populations for 2015 revealed BMI was significantly higher in Frankfurt, than in Moscow. A high BMI is a positive predictor for a better outcome[124,125] and decreased mortality[124]. Epidemiological analysis of normal German[104] and Russian[105-107] population didn´t explain this severe gap (referred to 3.6.). In the same way both FEV1 populations of 2015 obtained with the R-program to get comparable samples showed Frankfurt CF-patients have a closer to normal FEV1 than Moscow CF-patients. A better FEV1 is associated with a better outcome[124] and a lower mortality. Subsequently these data indicate Frankfurt patients should have a better outcome than Moscow patients.

Our results have to be interpreted with caution, because our data range is very small and incomplete for the years before 2015 and in particular before 2010. To better describe the differences between both CF-centers and both CF-populations a study with a broader perspective should be started to verify if this gap is maintained over a longer period of time (three to five years). The evaluation of the necessity of intravenous antibiotic treatment has also to be examined and the observed better values for Frankfurt have to be proved statistically. The relation between the necessity of intravenous antibiotic therapy and a worse outcome for CF-

patients has to be discussed. A study published in 2015 questioned the link between both and put other antibiotic treatments (oral therapy or inhaled therapy) on the same acting level[126]. Subsequently, other antibiotic therapies have to be considered and data should be collected about them. Another broader study should examine mortality in both centers to prove the impact of the surrogate markers, which has been described[43].

Furthermore, the reasons of these gaps in surrogate markers for CF prognosis have to be investigated. One possible cause could be a possible difference in F508del mutation or other CF-specific gene mutation distribution[1]. These data should be collected in a further study. Moreover, epidemiologic reasons should be regarded in a larger scale and also compared and evaluated in another study. Socioeconomic differences between both countries should also be considered and could be explanations for gaps between both CF-patient populations. Nevertheless they should be nuanced by a comparison with socioeconomic status of normal populations. In particular, different types of drugs, modes of application, frequency of application, treatment regimens and the availability of medication could play a role. Other reasons that must be considered in further studies are the different therapeutic approaches and the differences in care in both countries.

In summary, we have identified that Frankfurt CF patients values for surrogate parameters of CF outcome were closer to normal than those in Moscow patients in a short time. Further studies should verify this difference on a longer lapse of time including larger data spectrum. First, this will allow to establish a hypothesis explaining this difference. Secondly, this could help to refine therapeutic approaches and to definite new recommendations.

6. Appendix

A)

Examination	Number of Patients		Average BMI		Median BMI	
Year	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	2	0	21.52	-	21.52	-
1991	2	1	21.54	14.49	21.54	14.49
1992	1	2	21.50	16.27	21.50	16.27
1993	2	7	20.91	16.44	20.91	15.08
1994	1	11	20.02	17.34	20.02	17.16
1995	10	7	16.66	17.36	16.11	17.16
1996	30	10	18.84	16.91	18.52	17.39
1997	35	23	19.41	17.61	19.55	17.72
1998	46	38	19.89	16.34	19.66	16.45
1999	45	39	19.97	17.33	19.13	17.65
2000	30	45	20.29	16.98	19.09	16.53
2001	14	53	19.07	16.79	18.05	16.85
2002	16	64	18.78	17.41	18.02	17.54
2003	68	78	21.43	17.42	20.85	17.55
2004	75	103	21.48	17.49	20.76	17.57
2005	13	101	20.57	18.04	20.68	18.03
2006	13	124	20.95	18.02	21.27	17.96
2007	13	160	20.51	18.11	21.10	18.13
2008	91	179	21.69	18.38	21.01	18.55
2009	84	188	22.39	18.55	21.81	18.52
2010	132	192	21.20	18.76	20.70	18.69
2011	137	199	21.40	18.71	21.14	18.47
2012	131	250	21.80	18.79	21.62	18.51
2013	130	263	21.99	18.68	21.66	18.29
2014	133	278	22.12	18.78	21.73	18.52

2015	141	301	22.24	18.74	21.63	18.59

Year	BMI standard deviation (SD)		BMI maximum		BMI minimum	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	0.64	-	21.98	-	21.07	-
1991	1.13	-	22.34	14.49	20.75	14.49
1992	-	1.75	21.50	17.51	21.50	15.03
1993	1.26	2.88	21.80	20.93	20.02	13.22
1994	-	3.82	20.02	25.00	20.02	13.34
1995	2.29	2.37	20.64	22.21	13.68	15.43
1996	3.17	2.21	25.83	19.37	14.07	13.47
1997	3.18	2.49	28.22	22.77	13.71	13.34
1998	3.18	3.58	27.64	22.77	13.65	1.92
1999	3.52	2.51	31.11	22.94	14.88	12.63
2000	4.89	2.71	37.56	24.15	13.13	12.70
2001	4.02	2.69	27.76	22.76	14.60	12.40
2002	2.94	2.65	24.01	23.23	14.74	11.65
2003	3.76	2.70	33.30	23.61	13.98	11.65
2004	4.05	2.77	35.50	24.88	12.93	10.82
2005	3.22	2.76	26.35	25.86	13.73	12.02
2006	3.35	2.83	26.67	25.72	14.38	12.03
2007	3.58	2.73	24.97	25.62	13.89	12.73
2008	4.10	2.79	40.75	26.23	14.38	11.83
2009	4.41	2.78	44.29	26.03	15.34	12.80
2010	4.20	2.84	45.35	30.03	14.27	12.60
2011	4.18	2.90	45.52	31.99	14.35	12.47
2012	4.03	2.69	45.34	27.73	13.86	12.47
2013	4.04	2.80	44.47	27.73	13.86	10.85
2014	4.17	2.86	45.41	31.46	14.10	13.02
2015	4.13	2.78	46.60	31.46	14.17	11.33

Year	BMI range		BMI 1st quartile		BMI 3rd quartile	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	0.91	-	-	-	-	-
1991	1.59	0.00	-	-	-	-
1992	0.00	2.48	-	-	-	-
1993	1.78	7.71	-	14.49	-	18.42
1994	0.00	11.66	-	14.22	-	19.30
1995	6.96	6.78	15.21	15.64	17.29	17.70
1996	11.76	5.90	16.51	15.35	20.88	18.85
1997	14.51	9.43	17.38	15.89	20.87	19.12
1998	13.99	20.85	17.93	14.22	21.60	18.46
1999	16.23	10.32	17.79	15.41	21.72	19.00
2000	24.43	11.45	17.59	14.81	21.15	19.23
2001	13.16	10.36	15.90	14.66	21.14	18.67
2002	9.27	11.58	16.76	15.23	21.38	18.93
2003	19.33	11.96	19.03	15.23	22.92	19.11
2004	22.57	14.06	19.23	15.21	23.00	19.47
2005	12.61	13.85	19.33	16.37	22.01	19.68
2006	12.29	13.69	19.76	15.66	22.60	19.82
2007	11.08	12.89	20.48	16.28	22.92	19.91
2008	26.37	14.40	19.58	16.47	22.80	20.09
2009	28.95	13.22	20.03	16.71	23.46	19.93
2010	31.08	17.43	18.81	16.97	22.95	20.20
2011	31.17	19.53	19.05	16.93	23.13	20.45
2012	31.48	15.27	19.34	16.86	23.29	20.45
2013	30.61	16.88	19.58	16.82	23.69	20.43
2014	31.32	18.44	19.31	16.86	23.81	20.50
2015	32.43	20.13	19.31	16.82	24.14	20.32

B)

Year	Number of patient data		FEV1 average		FEV1 median	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	2	0	3800	-	3800	-
1991	2	0	3590	-	3590	-
1992	1	1	4370	2820	4370	2820
1993	2	4	3600	1280	3600	1000
1994	1	8	2550	1706.25	2550	1210
1995	6	6	2136.67	1216.67	2030	1155
1996	27	6	1825.93	1783.33	1800	1685
1997	34	19	2150.88	1998.42	2070	1640
1998	42	24	2357.62	1783.33	2090	1350
1999	44	28	2244.32	2215.00	2205	1980
2000	28	25	2512.86	2193.20	2555	2300
2001	13	30	2333.85	2019.67	2120	1955
2002	17	37	2328.82	2026.76	2090	1920
2003	66	50	2439.39	2186.00	2320	2000
2004	71	67	2447.89	2221.34	2340	2020
2005	15	73	2366.67	2296.71	2350	2030
2006	13	87	2571.54	2202.41	2450	2040
2007	13	125	2728.46	2301.36	2480	2130
2008	93	155	2354.73	2247.81	2230	2010
2009	86	171	2488.72	2299.30	2450	2220
2010	133	169	2463.91	2270.77	2270	2120
2011	137	176	2446.93	2192.33	2300	2090
2012	133	234	2437.44	2136.54	2230	2030
2013	135	251	2450.67	2120.84	2370	2020
2014	135	275	2426.81	2057.35	2310	1900
2015	145	295	2460.34	1983.12	2290	1850

Year	FEV1 standard deviation (SD)		FEV1 maximum		FEV1 minimum	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	565.69	-	4200	-	3400	-
1991	1343.50	-	4540	-	2640	-
1992	-	-	4370	2820	4370	2820
1993	1173.80	671.71	4430	2280	2770	840
1994	-	1290.10	2550	4390	2550	610
1995	638.55	647.79	3320	2420	1520	600
1996	512.72	1070.49	3090	3180	920	630
1997	726.81	1160.03	3960	4060	870	610
1998	883.31	1036.85	4400	3820	1090	570
1999	821.57	1126.85	4310	5020	130	580
2000	906.30	948.37	4080	3810	900	870
2001	1041.78	1000.76	4330	4330	560	570
2002	1053.90	905.15	4540	4060	600	660
2003	1027.37	1044.13	5820	4510	500	600
2004	908.67	1063.67	4870	4790	570	480
2005	1074.40	1141.05	4530	6490	920	460
2006	930.45	1036.96	4530	5980	960	610
2007	1053.31	1043.37	4590	5650	1340	510
2008	971.57	1114.60	5030	5870	580	380
2009	1055.56	1073.32	5440	6240	560	480
2010	1036.99	981.22	5390	5390	710	730
2011	1028.96	1036.40	5440	5080	650	420
2012	1023.65	1036.54	5130	6420	580	450
2013	1015.53	1034.53	5300	6400	690	500
2014	1042.62	990.51	5370	5130	730	192
2015	1112.38	985.01	5410	5220	600	520

Year	FEV1 range		FEV1 1st quartile		FEV1 3rd quartile	
	Frankfurt	Moscow	Frankfurt	Moscow	Frankfurt	Moscow
1990	800	-	-	-	-	-
1991	1900	-	-	-	-	-
1992	0	0	-	2820	-	2820
1993	1660	1440	-	930	-	1350
1994	0	3780	-	870	-	1972.5
1995	1800	1820	1755	807.5	2200	1247.5
1996	2170	2550	1515	892.5	2060	2590
1997	3090	3450	1720	1090	2517.5	2975
1998	3310	3250	1772.5	975	2897.5	2472.5
1999	4180	4440	1775	1357.5	2607.5	3085
2000	3180	2940	1760	1230	3402.5	2740
2001	3770	3760	1520	1135	3000	2655
2002	3940	3400	1600	1280	3090	2540
2003	5320	3910	1755	1262.5	3157.5	2807.5
2004	4300	4310	1805	1405	2915	2865
2005	3610	6030	1805	1540	2790	2710
2006	3570	5370	2030	1500	2870	2695
2007	3250	5140	1920	1680	3440	2840
2008	4450	5490	1670	1370	2940	2985
2009	4880	5760	1732.5	1455	2980	3045
2010	4680	4660	1690	1560	2980	2970
2011	4790	4660	1680	1355	2960	2890
2012	4550	5970	1670	1332.5	3060	2820
2013	4610	5900	1690	1315	2975	2730
2014	4640	4938	1690	1230	2895	2785
2015	4810	4700	1600	1245	3280	2585

C)

Year	Number of Patient data		Necessity of intravenous antibiotic therapy	
	Frankfurt	Moscow	Frankfurt	Moscow
1990	24	1	1	0
1991	24	2	1	0
1992	25	3	1	1
1993	26	9	1	2
1994	26	15	1	3
1995	27	12	3	4
1996	27	15	2	4
1997	27	26	2	8
1998	30	43	6	15
1999	31	44	6	18
2000	33	54	7	20
2001	36	61	10	19
2002	41	83	21	26
2003	48	90	25	31
2004	58	111	32	44
2005	63	118	27	46
2006	66	147	24	64
2007	69	180	32	79
2008	90	209	43	99
2009	98	201	35	97
2010	118	209	47	100
2011	130	222	49	105
2012	130	256	48	130
2013	139	270	52	143
2014	142	274	57	167
2015	148	295	58	191

Year	Percentage of necessity of intravenous antibiotic therapy	
	Frankfurt	Moscow
1990	4.17	0.00
1991	4.17	0.00
1992	4.00	33.33
1993	3.85	22.22
1994	3.85	20.00
1995	11.11	33.33
1996	7.41	26.67
1997	7.41	30.77
1998	20.00	34.88
1999	19.35	40.91
2000	21.21	37.04
2001	27.78	31.15
2002	51.22	31.33
2003	52.08	34.44
2004	55.17	39.64
2005	42.86	38.98
2006	36.36	43.54
2007	46.38	43.89
2008	47.78	47.37
2009	35.71	48.26
2010	39.83	47.85
2011	37.69	47.30
2012	36.92	50.78
2013	37.41	52.96
2014	40.14	60.95
2015	39.19	64.75

Table 10: ***A)*** *BMI biometrical descriptive statistics from 1990 to 2015 including number of patient data sets, average BMI, median BMI, SD (standard deviation) BMI, maximum BMI, minimum BMI, BMI range, 1st quartile BMI and 3rd quartile BMI.*

B) *FEV1 biometrical descriptive statistic from 1990 to 2015 including number of patient data, average FEV1, median FEV1, SD (standard deviation) FEV1, maximum FEV1, minimum FEV1, FEV1 range, 1st quartile FEV1 and 3rd quartile FEV1.*

C) *Biometrical descriptive statistic analysis of necessity of intravenous antibiotic therapy from 1990 to 2015 including number of patient data, number of necessity of intravenous antibiotic therapy and percentage of necessity of intravenous antibiotic therapy.*

Conflict of interest statement

The authors have declared that no conflict of interest exists.

Declarations of interest

None.

Summary

Background

Previous studies have demonstrated that CF prognosis is dependent of three major parameters: FEV1, BMI and need of intravenous antibiotic therapy. The CF centres of Frankfurt, Germany, and Moscow, Russia, care for cystic fibrosis patients from childhood through adult age. We decided to investigate and compare both centers for the three most important CF prognostic parameters (BMI, FEV1, need of intravenous antibiotics) from 1990 to 2015. Differences in these three parameters have an influence on CF lifetime prognosis and have to be examined. No comparable study has been published so far.

Methods

German patient data was collected from the national cystic fibrosis database “Muko.web”. Missing values were extracted from the Hospital Information System (Orbis serving as the medical record data bank of the University Hospital in Frankfurt). Russian patient data were taken directly from the medical records in Moscow and, after they had been anonymized, they were handed over and merged in a table with the German patient data. In a descriptive statistical analysis with Bias and R Studio the values were compared.

Results

428 patients from Moscow (217 male, 211 female; 348 (81,3%) were P. aeruginosa positive) and 159 patients from Frankfurt (92 male, 67 female; 137 (86,2%) with P. aeruginosa positive) were compared with regard to P. aeruginosa positivity, BMI, FEV1 and need of intravenous antibiotic therapy. A difference was observed in both prognostic parameters FEV1 and BMI for 2015; CF patients in Moscow stratified by age groups had lower BMI than CF patients in Frankfurt (age 16-18: $p=0,003$; age 19-22: $p=0,004$; age 23-29: $p<0,001$; age 30-35: $p<0,001$; age 36-66: $p=0,024$). In a matching pairs analysis including 100 patients from Frankfurt and

100 patients from Moscow for the year 2015 FEV1 was significantly lower in Moscow patients ($p<0,001$).

Conclusions

This study showed a significant difference in prognostic parameters between Frankfurt and Moscow in the cross-sectional analysis for the year 2015. A further study should evaluate this difference to show whether this difference will be found over a longer period of time and how relevant it is. The reason for this prognostic gap between patients in Moscow and Frankfurt could be epidemiological, socioeconomic, based on a difference in genetics (F508del mutation prevalence), but could as well be based on a difference in care or on different therapeutic approaches and should be investigated in a broader study. After this study modifications in treatment plans, medical investments or/and therapeutic approaches can be modified to influence positively the lifetime prognosis of patients in centers with a worse outcome.

Zusammenfassung

Hintergrund

Frühere Studien haben gezeigt, dass die Prognose von CF-Patienten von drei Parametern abhängt. Es handelt sich hierbei um die FEV1, den BMI und die Notwendigkeit einer intravenösen Antibiotikatherapie. Die CF-Zentren in Frankfurt (Deutschland) und Moskau (Russland) betreuen Mukoviszidose-Patienten vom Lebensbeginn an bis hin zum Lebensende. Wir haben uns entschlossen in beide Zentren die drei wichtigsten prognostischen CF-Parameter (BMI, FEV1, Notwendigkeit einer intravenösen Antibiotikatherapie) von 1990 bis 2015 zu erheben und zu vergleichen. Unterschiede in diesen drei Parametern haben einen starken Einfluss auf die Lebenszeitprognose der CF-Patienten und müssen untersucht werden. Bisher wurde keine vergleichbare Studie durchgeführt und veröffentlicht.

Methoden

Deutsche Patientendaten wurden aus der nationalen Mukoviszidose-Datenbank „Muko.web“ erhoben. Fehlende Werte wurden aus dem Krankenhausinformationssystem (Orbis als Datenbank des Universitätsklinikums Frankfurt) extrahiert. Russische Patientendaten wurden direkt aus den Krankenakten in Moskau entnommen und nach ihrer Anonymisierung übermittelt. Schließlich wurden die Daten aus beiden Zentren in einer Tabelle zusammengeführt. In einer deskriptiven statistischen Analyse mit Bias und R Studio wurden die Werte anschließend verglichen.

Ergebnisse

428 Patienten aus Moskau (217 Männer, 211 Frauen; 348 (81,3%) waren P. aeruginosa-positiv) und 159 Patienten aus Frankfurt (92 Männer, 67 Frauen; 137 (86,2%) mit P. aeruginosa-positiv) wurden in Hinsicht auf der P. aeruginosa Präsenz, dem BMI, der FEV1 und der Notwendigkeit einer intravenösen Antibiotikatherapie verglichen. Ein Unterschied wurde sowohl bei den prognostischen Parametern FEV1 als auch beim BMI für 2015 beobachtet. Nach Altersgruppen geschichtete CF-Patienten in Moskau hatten einen niedrigeren BMI als CF-Patienten in

Frankfurt (Alter 16-18: p = 0,003; Alter 19-22: p = 0,004; Alter 23-29: p <0,001; Alter 30-35: p <0,001; Alter 36-66: p = 0,024). In einer Matching-Pair-Analyse mit 100 Patienten aus Frankfurt und 100 Patienten aus Moskau für das Jahr 2015 war die FEV1 bei Moskauer Patienten signifikant niedriger (p <0,001).

Schlussfolgerungen

Diese Studie zeigte einen signifikanten Unterschied in den prognostischen Parametern zwischen Frankfurt und Moskau für das Jahr 2015 in einer Querschnittsanalyse. Eine weitere Studie sollte diesen Unterschied über einen längeren Zeitraum nachweisen, damit festgestellt werden kann inwiefern dieser Unterschied relevant ist. Die Ursache dieser Unterschiede könnte auf einen oder mehrere Faktoren beruhen. Diskutiert werden epidemiologische, sozioökonomische (finanzielle Mittel, sowie Verteilung der Pflegeeinrichtungen und der Pflegemittel), genetische (F508del-Mutationsverteilung), pflegerische, therapeutische und medikamentöse Ansätze, die wiederum in einer weiteren Studie untersucht werden sollten. Abhängig von den Ergebnissen dieser Studie könnten Veränderungen in den Behandlungsplänen, in der Umverteilung medizinischer Investitionen und/oder in den therapeutischen Ansätzen erfolgen, um die Lebenszeitprognose von CF-Patienten in Zentren mit schlechteren Prognoseparametern positiv zu beeinflussen.

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Danke für die Rückenstärkung und die Motivation auch an meinen sehr guten Freund - Florian Schneider -, der mir mit Rat immer zur Seite stand, wenn ich es

nötig hatte und mir auch spät abends bei Diskussionen am Telefon Veränderungsvorschläge bot.

Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Comparison of surrogate parameters of prognosis (BMI, FEV1 and need of intravenous antibiotic therapy) between CF-patients with and without P. aeruginosa in Frankfurt and Moscow from 1990 to 2015

in dem Christiane Herzog CF-Zentrum, Pneumologie, Medizinische Klinik I unter Betreuung und Anleitung von Prof. Dr. Thomas O.F. Wagner mit Unterstützung durch Dr. Christina Smaczny ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht*. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

_____ _____

(Ort, Datum) (Unterschrift)

*) im Falle des Nichtzutreffens entfernen

Ethikvotum

Das Ethikvotum zur retrospektiven Studie wurde von der Ethik-Kommission des Fachbereichs Medizin des Universitätsklinikums der Goethe-Universität Frankfurt am Main am 23.05.2017 genehmigt. Es bestanden keine berufsrechtlichen und berufsethischen Bedenken zur Durchführung der Studie und der Dissertation.

FACHBEREICH MEDIZIN FRANKFURT
GOETHE-UNIVERSITÄT

KLINIKUM der J. W. Goethe-Universität Frankfurt a. M.
Eing. 23. MAI 2017
Abt. Pneumologie

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IM HAUSE
Medizinische Klinik I
Pneumologie / Allergologie
Herr Prof. Dr. Thomas Wagner

KLINIKUM der J. W. Goethe-Universität Frankfurt a. M.
Eing. 23. MAI 2017
Abt. Pneumologie

Ethik-Kommission

Vorsitz:
Prof. Dr. Sebastian Harder

Geschäftsführung:
Dr. Annette Malsch

Bearbeitung des Vorgangs:
Stemler

Montag, 22. Mai 2017

Geschäfts-Nr.: 183/17 (Bitte stets angeben!)
Titel: Vergleich der Surrogatmarker (BMI, FEV1 und Notwendigkeit einer intravenösen Antibiotikatherapie) von Mukoviszidosepatienten mit und ohne Pseudomonas aeruginosa-Nachweis in Frankfurt und einem anderen Standort zwischen 1990 und 2015

VOTUM

Sehr geehrter Herr Professor Wagner,

vielen Dank für die Zusendung der Studienunterlagen vom 25.04.2017.

Es bestehen **keine berufsrechtlichen und berufsethischen Bedenken**. Die Ethik-Kommission erteilt eine **zustimmende Bewertung**.

Hinweise:
1. Wir gehen davon aus, dass der Erfassungszeitraum auf 1990-2015 begrenzt ist.
2. Die Ethik-Kommission weist darauf hin, dass bei der Einsichtnahme der Unterlagen § 12 Hessisches Krankenhausgesetz in Verbindung mit § 33 Hessisches Datenschutzgesetz eingehalten werden muss.

Eine Information über den Abschluss der Studie wird erbeten.

Mit freundlichen Grüßen

S. Harder

Prof. Dr. med. Sebastian Harder
Vorsitzender der Ethik-Kommission

Vorgelegte Unterlagen:
- Protokoll, V.1.0 vom 25.04.2017

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9:00 bis 15:30 Uhr

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Aus Wissen wird Gesundheit.

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Interne Buchungsanweisung
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Sehr geehrter Herr Stenzel,

bitten führen Sie folgende Buchung innerhalb des F&L Kontenkreises durch:

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Mit freundlichen Grüßen

i.A. Stml

Dr. Annette Malsch
Geschäftsführerin der Ethik-Kommission

cc: Prof. Dr. TOF Wagner, ZIM

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