Zborník prednášok
z V4-CF konferencie

Book of Presentations from V4-CF Conference

2 CONFERENCE

V4-CF

17 - 18 November 2017
Kraków, Wieliczka

Where are we?
Where are we going?






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FUNDACJA POMOCY RODZINOM I CHORYM NA MUKOWISCYDOZĘ

SLOVENSKÁ ASOCIÁCIA CYSTICKEJ FIBRÓZY

Zborník prednášok z V4-CF konferencie

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O B S A H

V4 CF Conference – Conference for "Salty children " in "SALTY MINE"

Dear friends,

last November I was lucky to be able to participate in the V4 CF conference in Kraków. It is amazing that teams from different countries working with cystic fibrosis have the opportunity to meet and exchange experience. It surely must put a strain on the organisers, but it is truly worth it. In Kraków, I met old acquaintances and got to know several new colleagues with much enthusiasm for the work with cystic fibrosis. The whole meeting had excellent organisation on very special place in Salty mine in Wieliczka and was of great benefit to all the participants.

I have spent more than 50 years of my life around people suffering from cystic fibrosis – the "salty children". It has not always been easy; especially in the early years we did not have enough medication and medical devices and thus many children were dying. I am incredibly happy that towards the end of my life I have lived to witness the enormous progress that has been made in the treatment and prognosis of this disease, but also to see that in my country and elsewhere in the world there are a great many young and enthusiastic people working with cystic fibrosis. Life with cystic fibrosis has not always been an easy one, but I am immensely grateful to have lived it. I have known many amazing and brave "salty" children, adolescents and their families and this has taught me to view life values differently from the way I had been used to.
I wish all the members of V4 countries much fulfillment and success in their work with cystic fibrosis and recognition for their work.

With love

V listopadu minulého roku jasem měla to štěstí, že jsem se mohla účastnit zasedání V4 CF konference v Krakově. Je skvělé, že se mohou týmy pracovníků, kteří se zabývají CF v různých zemích, setkávat a vyměňovat si své zkušenosti. Na organizátory to jistě klade veliký nárok, ale opravdu to stojí za to. Setkala jsem se v Krakově jak se starými známými tak jsem poznala řadu nových a pro práci s CF nadšených kolegyň a kolegů. Celé setkání bylo skvěle organizováno, na velice specifickém místě v Solné bani ve Wieliczke a bylo velkým přínosem pro všechny zúčastněné.

S nemocnými s CF jsem strávila víc než 50 let života. Nebylo to vždy lehké; hlavně v prvních letech jsme neměli dost léků a pomůcek a mnoho dětí nám umíralo. Jsem nesmírně šťastná, že jsem se na sklonku svého života dočkala obrovského pokroku v léčbě, zlepšení prognózy tohoto onemocnění i toho, že se našlo nejen u nás ale i jinde ve světě mnoho mladých, nadšených lidí, kteří se CF věnují.
Život s CF nebyl vždy lehký, ale jsem nesmírně vděčná, že jsem ho mohla prožít. Poznala jsem řadu báječných statečných "slaných" dětí i dospívajících a jejich rodin a naučila jsem se jinak, než jsem dosud byla zvyklá, posuzovat životní hodnoty.

Přeji všem členům V4, aby se jim práce s CF dařila, aby je těšila a přinášela úspěch.

S láskou

Doc. MUDr. Věra Vávrová, DrSc., Prague

CZECH NATIONAL PLAN FOR RARE DISEASES AND ITS IMPACT PHARMACOECONOMIC STUDIES IN CF

Prof. MUDr. Milan MACEK, Dr.Sc., Department of Biology and Medical Genetics, Charles University Prague and 2 Faculty of Medicine, University Hospital Motol, PRAGUE, CZ

Rare diseases (RD)

1/ Prevalence **1 in 2000** individuals (CE 141/2000)
2/ Strong genetic component (~ 80%)
3/ „Mendelian / Orphan“ diseases
4/ Limited prognosis „quoad vitam“:
35% mortality < 1Y, 10% 1-5Y a 12% 5-15Y
5/ Approx. 5000 clinical entities, about 1200 if single case reports are disregarded – (~ 20 mil. in v EU28)
6/ Only 200 RD are listed in ICD10
7/ Issues: awareness, diagnosis, referral, medical social care, financing of care personalised med.
8/ Intl. Cooperation (EU / EEA–Norway Grants; USA)
9/ European Reference Networks

Cystic fibrosis serves as a model.

CZ-National strategy 2010-2020

VLÁDA ČESKÉ REPUBLIKY

USNESENÍ

VLÁDY ČESKÉ REPUBLIKY
ze dne 14. června 2010 č. 466

o Národní strategii pro vzácná onemocnění
na léta 2010-2020

Vláda

I. **schvaluje** Národní strategii pro vzácná onemocnění na léta 2010-2020, obsaženou v části III materiálu č.j. 593/10 (dále jen „Národní strategie“);

II. **ukládá**

1. členům vlády plnit Národní strategii,

2. ministryni zdravotnictví ustavit meziresortní a mezioborovou pracovní skupinu, která připraví Národní akční plán pro vzácná onemocnění na léta 2011-2013 a která bude koordinovat aktivity v oblasti vzácných onemocnění,

3. ministryni zdravotnictví ve spolupráci s ostatními členy vlády předložit vládě do 30. června 2011 Národní akční plán pro vzácná onemocnění na léta 2011-2013;

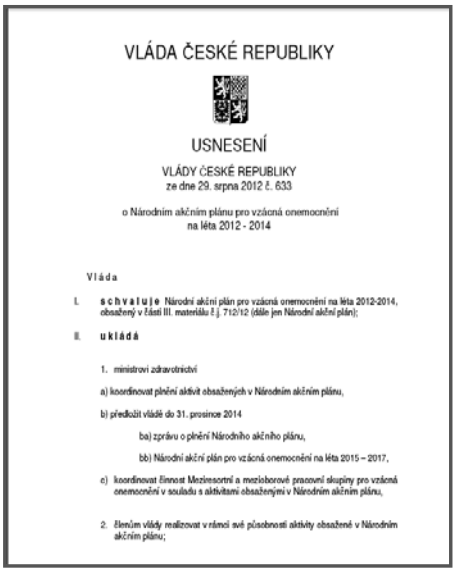
III. **doporučuje** hejtmanům ve spolupráci s orgány místní samosprávy a nevládními organizacemi do krajských rozvojových plánů zohlednit řešení problematiky vzácných onemocnění.

Provedou:
členové vlády

Na vědomí:
hejtmani,
primátor hlavního města Prahy

Předseda vlády
Ing. Jan Fischer, CSc., v. r.

CZ - National action plans 1+2



VLÁDA ČESKÉ REPUBLIKY

USNESENÍ

VLÁDY ČESKÉ REPUBLIKY
ze dne 29. srpna 2012 č. 633

o Národním akčním plánu pro vzácná onemocnění
na léta 2012 - 2014

V l á d a

I. **s c h v a l u j e** Národní akční plán pro vzácná onemocnění na léta 2012-2014, obsažený v části III. materiálu č.j. 712/12 (dále jen Národní akční plán);

II. **u k l á d á**

1. ministrovi zdravotnictví

a) koordinovat plnění aktivit obsažených v Národním akčním plánu,

b) předložit vládě do 31. prosince 2014

ba) zprávu o plnění Národního akčního plánu,

bb) Národní akční plán pro vzácná onemocnění na léta 2015 – 2017,

c) koordinovat činnost Mezirezortní a meziborové pracovní skupiny pro vzácná onemocnění v souladu s aktivitami obsaženými v Národním akčním plánu,

2. členům vlády realizovat v rámci své působnosti aktivity obsažené v Národním akčním plánu;

VLÁDA ČESKÉ REPUBLIKY

USNESENÍ

VLÁDY ČESKÉ REPUBLIKY
ze dne 4. února 2015 č. 76

ke Zprávě o plnění úkolů vyplývajících z Národního akčního plánu
pro vzácná onemocnění na léta 2012 až 2014
a k Národnímu akčnímu plánu pro vzácná onemocnění na léta 2015 až 2017

Vláda

I. **schvaluje** Zprávu o plnění úkolů vyplývajících z Národního akčního plánu pro vzácná onemocnění na léta 2012 až 2014 a Národní akční plán pro vzácná onemocnění na léta 2015 až 2017, uvedené v části III materiálu čj. 69/15;

II. **ukládá** ministru zdravotnictví předložit vládě do 31. prosince 2017

1. Zprávu o plnění úkolů vyplývajících z Národního akčního plánu pro vzácná onemocnění na léta 2015 až 2017,

2. návrh Národního akčního plánu pro vzácná onemocnění na léta 2018 až 2020.

Provede:
ministr zdravotnictví

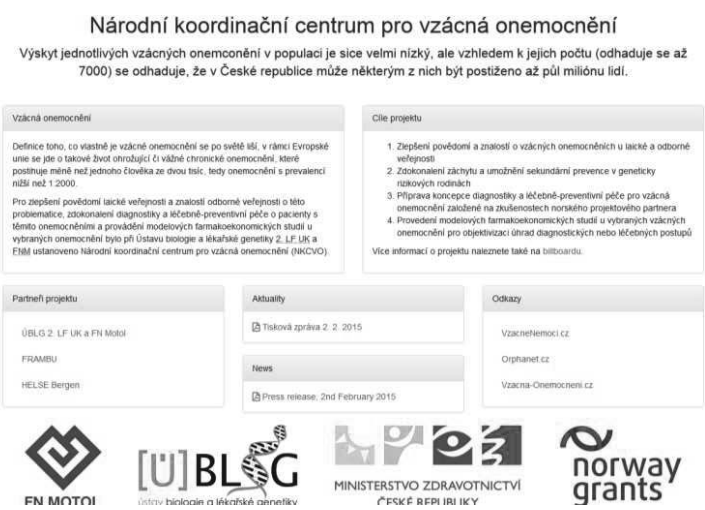
Předseda vlády
Mgr. Bohuslav Sobotka, v. r.

CZ - National Action Plans for Rare Diseases (2015-2017)

Tasks:

1. **Improved awareness on RD**
2. **Education of lay public and physicians in RD**
3. **Prevention of RD and diagnostic guidelines**
4. **Broadening of newborn screening**
5. **Improvement of availability and quality of care in RD**
6. **Improvement of social care and inclusion**
7. **Support of research**
8. **Biobanking**
9. **Empowerment of patient associations**
10. **Inter-ministerial and interdisciplinary collaboration**
11. **International collaboration**

CZ- National coordination centre for rare diseases



www.nkcvo.cz

Czech national patient alliance

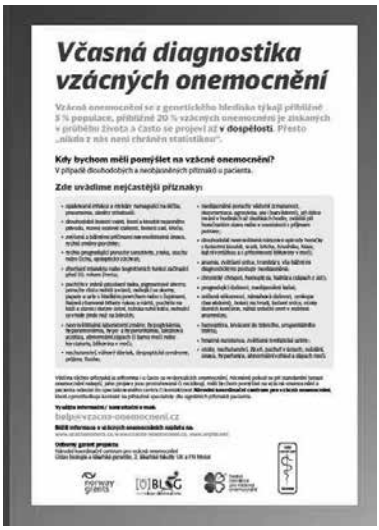
www.vzacna-onemocneni.cz

37 more... + single families

Public polls on rare diseases 2014

http://www.aifp.cz/cs/aktuality/informace-pro-media/vzacna-onemocneni-jsou-pro-vetsinu-z-nas-velkou-neznamou/

Project „Early Diagnosis!



help@vzacna-onemocncni.cz

Patient testimonies / stories

Každá nákaza je nebezpečná: cystická fibróza

31.1.2016

V dýchacím ústrojí lidí s CF se velice snadno usazují bakterie. Takových bakterií se plíce zdravého člověka snadno zbaví, ale nemocným s CF poškozují plíce. Musejí se proto vyhýbat všem zdrojům možné nákazy, třeba i MHD. Pacienti s CF se také nesmějí vídat mezi sebou, aby si navzájem nepředali nebezpečné bakterie.

Pokračování

VLÁDNÍ VÝBOR PRO ZDRAVOTNĚ POSTIŽENÉ OBČANY

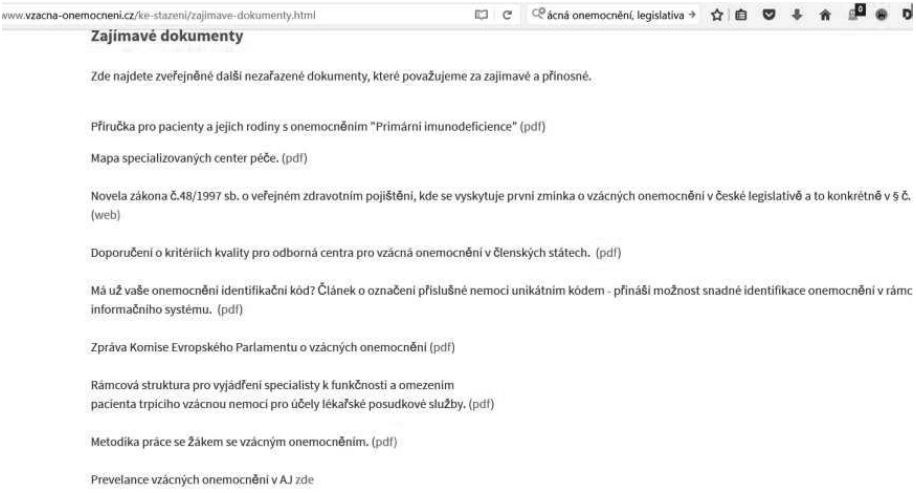
České asociaci pro vzácná onemocnění, z. s.

VZÁCNÍ
(O ŽIVOTĚ SE VZÁCNÝMI ONEMOCNĚNÍMI)

I. cenu

www.vzacni.cz

Online resources-Helpmail



www.vzacna-onemocneni.cz/ke-stazeni/zajimave-dokumenty.html

ácná onemocnění, legislativa

Zajímavé dokumenty

Zde najdete zveřejněné další nezařazené dokumenty, které považujeme za zajímavé a přínosné.

Příručka pro pacienty a jejich rodiny s onemocněním "Primární imunodeficience" (pdf)

Mapa specializovaných center péče. (pdf)

Novela zákona č.48/1997 sb. o veřejném zdravotním pojištění, kde se vyskytuje první zmínka o vzácných onemocnění v české legislativě a to konkrétně v § č. (web)

Doporučení o kritériích kvality pro odborná centra pro vzácná onemocnění v členských státech. (pdf)

Má už vaše onemocnění identifikační kód? Článek o označení příslušné nemoci unikátním kódem - přináší možnost snadné identifikace onemocnění v rámc informačního systému. (pdf)

Zpráva Komise Evropského Parlamentu o vzácných onemocnění (pdf)

Rámcová struktura pro vyjádření specialisty k funkčnosti a omezením pacienta trpícího vzácnou nemocí pro účely lékařské posudkové služby. (pdf)

Metodika práce se žákem se vzácným onemocněním. (pdf)

Prevelance vzácných onemocnění v AJ zde

http://www.vzacna-onemocneni.cz/ke-stazeni/zajimave-dokumenty.html
Help@vzacnaonemocneni.cz

Improved awareness

Media presentations and campaigns for lay public and experts

Not only during the rare disease day !

14

Medical education in rare diseases

- **Collaboration with key medical schools (Prague, Brno, Olomouc)**
- **General practitioners – conferences – presentation**
- **Postgraduate education – physicians (www.ipvz.cz)**

15

Medical legislation 1.
Act 373/2011Coll

Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes

Strasbourg, 27.XI.2008

The Treaty of Lisbon amending the Treaty on European Union and the Treaty establishing the European Community entered into force on 1 December 2009. As a consequence, as from that date, any reference to the European Community shall be read as the European Union.

Zákon č. 373/2011 Sb., o specifických zdravotních službách

§ 28

(1) Genetické vyšetření zahrnuje klinické a genetické laboratorní vyšetření, slouží ke stanovení podílu variant v lidském genomu na rozvoj nemocí u vyšetřované osoby nebo jejích potomků. Lidským genomem se rozumí souhrn dědičných informací, které byly zděděny od předků nebo nově vznikly u vyšetřované osoby a mohou být předávány budoucím generacím. Genetickým laboratorním vyšetřením se rozumí laboratorní analýza struktury a funkce lidského genomu nebo jeho částí, která musí být indikována na základě jeho klinické oprávněnosti a užitečnosti pro vyšetřovanou osobu nebo budoucí generace. Provedení genetického laboratorního vyšetření musí být podrobně odůvodněno ve zdravotnické dokumentaci.

(2) Za genetické laboratorní vyšetření podle tohoto zákona se nepovažují vyšetření

a) prováděná za účelem posouzení vhodného dárce nebo příjemce krve, krevních složek, buněk, tkání nebo orgánů,

b) prováděná za účelem zjištění patogenních organismů vyskytujících se u člověka,

c) prováděná výhradně za účelem určení totožnosti jedince,

d) prováděná v rámci celoplošných screeningových programů řešených podzákonnými normami,

e) prováděná za účelem posouzení účinku genotoxických faktorů životního a pracovního prostředí.

Medical legislation 2- Act 48/1997 amended „Rights and obligations of insured individuals

PRÁVA A POVINNOSTI POJIŠTĚNCE

§ 11

(1) Pojištěnec má právo

a) na výběr zdravotní pojišťovny, nestanoví-li tento zákon jinak,

b) na výběr poskytovatele zdravotních služeb na území České republiky (dále jen „poskytovatel"), který je ve smluvním vztahu k příslušné zdravotní pojišťovně, a na výběr zdravotnického zařízení tohoto poskytovatele; v případě registrujícího poskytovatele může toto právo uplatnit jednou za 3 měsíce,

c) na časovou a místní dostupnost hrazených služeb poskytovaných smluvními poskytovateli příslušné zdravotní pojišťovny,

d) na poskytnutí hrazených služeb v rozsahu a za podmínek stanovených tímto zákonem, přičemž poskytovatel nesmí za tyto hrazené služby přijmout od pojištěnce žádnou úhradu,

e) na léčivé přípravky a potraviny pro zvláštní lékařské účely bez přímé úhrady, jde-li o léčivé přípravky a potraviny pro zvláštní lékařské účely hrazené ze zdravotního pojištění a předepsané v souladu s tímto zákonem; to platí i v případech, kdy poskytovatel lékárenské péče nemá se zdravotní pojišťovnou pojištěnce dosud uzavřenou smlouvu,

f) na poskytnutí zdravotní péče hrazené v rozsahu a za podmínek stanovených tímto zákonem související s onemocněními s velmi nízkým výskytem v populaci ve smyslu přímo použitelného právního předpisu Evropské unie[19a)] (dále jen „vzácná onemocnění"), včetně léčivých přípravků pro vzácná onemocnění, hrazených podle tohoto zákona,

g) na poskytnutí informací od zdravotní pojišťovny o jemu poskytnutých hrazených službách,

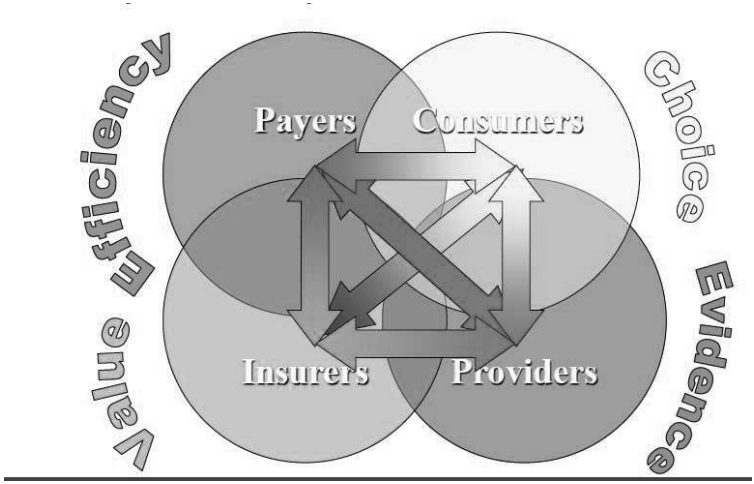
h) podílet se na kontrole poskytnuté zdravotní péče hrazené zdravotním pojištěním,

i) na vystavení dokladu o zaplacení regulačního poplatku podle § 16a,

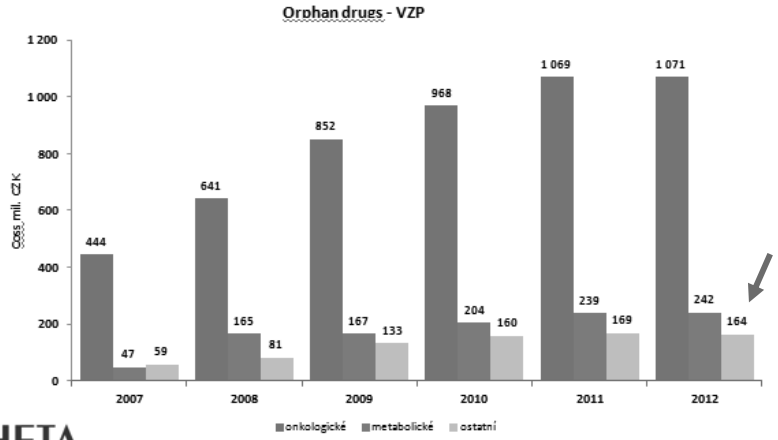
Nationwide Newborn Screening
18 disorders – 1:1000 detection rate

http://www.novorozeneckyscreening.cz/en

HE-branch of economics concerned with issues related to scarcity in the allocation of health and health care



CONSUMPTION OF ORPHAN DRUGS GENERAL HEALTH INSURANCE COMPANY (VZP)



HETA
Institute of Health Economics and Technology Assessment

Background

Analysis of the economic burden in CF is important for disease management
Assessment of **baseline (direct) costs prior to the introduction of CFTR modulating therapies for health insurance companies**
Assessment of cost effectivness and implemenation of CF treatment schemes

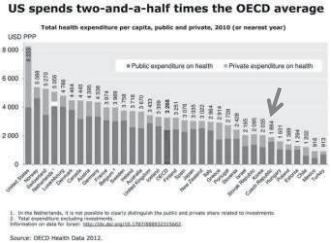
First author [ref.]	Study year	Study country	Patients n	Mean age years	Age range years	Mean annual cost# 2013 €
Robson [61]	1990	UK	119	21	16–44	15 461
Wildhagen [62]	1991	The Netherlands	81	14	0–37	16 325
Ireys [63]	1993	USA	204		0–18	14 466
Baumann [64]	1996	Germany	138		0–18	23 722
Johnson [65]	1996	Canada	303	18		5850
Lieu [66]	1996	USA	136	17	0–56	12 598
Horvais [67]	2001	France	65			15 674
Hout [68]	2003	France	64	15.3	0–48	27 725
Heimeshoff [59]	2004	Germany	212	20	0–adult	36 419
Eidt-koch [69]	2006	Germany	301			20 103
Ouyang [60]	2006	USA	1250		0–64	38 293
Dewitt [70]	2008	USA	352	14.6	5–adult	28 747
Van gool [71]	2009	Australia	2255	15.4		11 182

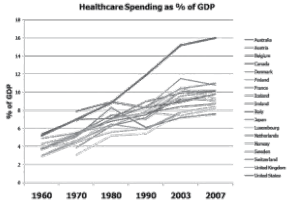
Klimeš et al. ERS Monogr 2014; 64: 304–319

Objectives- – „show me the evidence“

To assess the direct costs of CF within the CZ medical care
The **prevalence-based cost** of illness analysis was performed in relation previously identified „major cost drivers“:

- severity of CF lung disease (measured by FEV_1 % predicted)
- Age / gender
- BMI (reflecting underweight = general nutritional status)
- Presence of chronic sino-bronchial infections (*P. aeruginosa*)





Patients and Methods

Clinical and laboratory data from the national CF registry (www.cfregistr.cz)
Cost data from the health insurance (www.vzp.cz, www.szpcr.cz)
Overall, 245 CF randomly selected patients were stratified by their age, gender, BMI and BMI z-score, *P. aeruginosa* and FEV_1% („mild" ≥70; „moderate 40≤ and ≤70 and severe CF lung disease <40; % predicted)
Healthcare costs were considered within: a) inpatient care, b) medicinal products and devices (MPD) and c) Procedures (laboratory examinations, diagnostics and outpatient care)
All costs were in year 2010 prices, **prior to CFTR-MT**
Descriptive statistics, Multivariate regression analysis (generalized linear model – GLM)

Figure 1: Total mean (median) annual costs related to the overall disease severity (cost in € 2010)

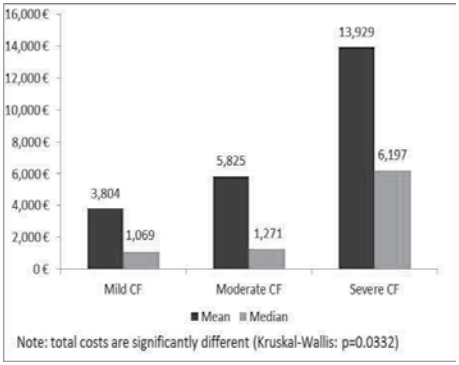
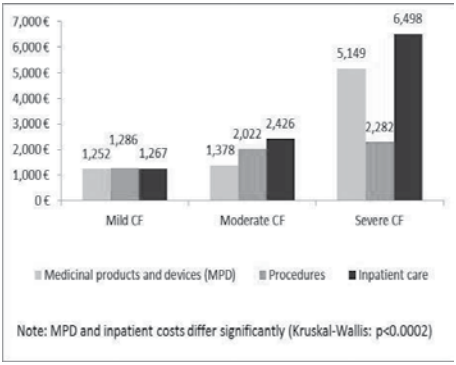
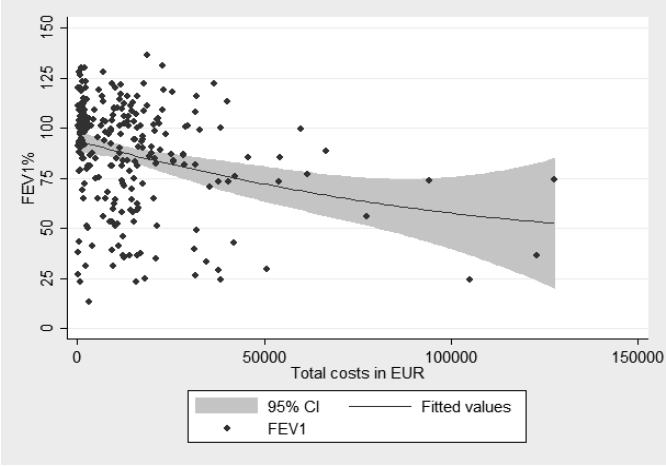


Figure 2: Mean annual costs of each cost component based on the disease severity (cost in € 2010)

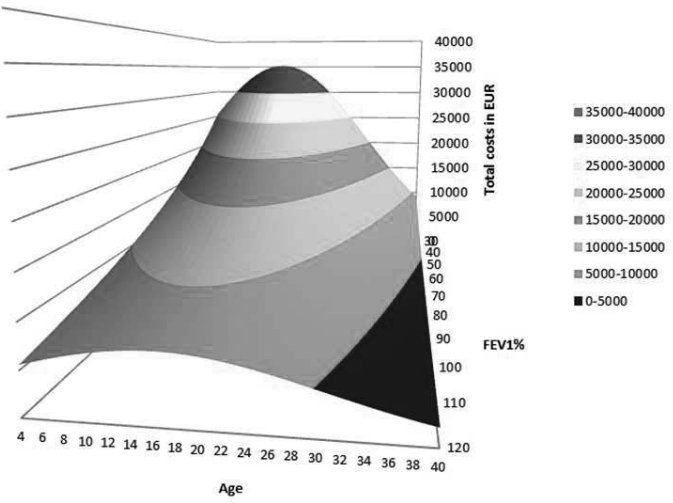


Distribution of costs according to FEV_1 %



Overall skewing due to outliers !

CF centre care „competition“- pediatric versus adults – case for the transition of car[illegible]



Current results are in accordance with current intl. studies

↓FEV1% by 1 pp = ↑ costs by ≈1% (transferrable marker !)

Increased disease severity = Increased costs (Van Gool et al.)

Comparable costs with other EU - **$19 647** a (adjustment for purchasing power parity - **$PPP 27 151)**

Valid outcomes for CZ and for dealing with health insurance

Table 1 – Summary of previous studies—health care cost of treating cystic fibrosis.

Source	Study year	Study country	Patients (n)	Mean age (y)	Age range (y)	Mean annual cost* (US $)
Robson et al. [5]	1990	UK	119	21	16-44	21,533
Wildhagen et al. [6]	1991	The Netherlands	81	14	0-37	22,757
Ireys et al. [7]	1993	USA	204		0-18	20,147
Baumann et al. [8]	1996	Germany	138		0-18	33,039
Johnson et al. [9]	1996	Canada	303	18		8,148
Lieu et al. [10]	1996	USA	136	17	0-56	17,546
Heimeshoff et al. [11]	2004	Germany	212	20	0- adult	30,723
Hervain et al. [12]	2005	France	65			21,830
Rib-Koch et al. [13]	2006	Germany	501			27,999
DeWitt et al. [14]	2008	USA	352	14.6	5- adult	40,037

* All originally reported national currencies converted to US $ at 2009 price levels applying OECD PPP conversion rates and using the CCEMG – EPPI-Centre Cost Converter (see http://eppi.ioe.ac.uk/costconversion/default.aspx); blank values, not stated.

Van Gool – ViH 2013

Table 1 Proposed criteria for evaluation of orphan drugs and corresponding potential parameters

Criteria	Price Differential		
	Lower	Medium	Higher
Rarity	1:2,000 - 1:20,000 or COMP figures > 3 in 10,000 (11%)	1:20,000 - 1:200,000 or COMP figures 1–3 in 10,000 (51%)	Less than 1:200,000 or COMP figures less than 1 in 10,000 (38%)
Level of research undertaken	Literature review	Building on previous existing knowledge	"Blue-sky" – starting research & development programme in an unknown area
Level of uncertainty of effectiveness	Immature, but promising data	Appropriate surrogate end-points	Robust clinical end-points
Manufacturing complexity	Not complex – small molecule / classic galenic form	Moderately complex	Highly complex biological and galenic form
Follow up measures (additional benefits and associated costs)	Moderate to none	Designed to answer specific, defined, delineated question	Safety and efficacy studies + size and duration of study
Characteristics without direct cost impact			
Disease severity	Morbidity	Mortality / severe invalidity in adulthood	Mortality / severe invalidity as infant
Available alternatives / unmet medical need	Alternatives with similar characteristics	Alternatives – but offering strong innovation to the disease treatment	No alternative
Level of impact on condition / disease modification	Low	Medium	Strong
Use in unique indication or not	Existing orphan or non-orphan indications for the same molecule*	Potential for multiple indications	Unique indication – no other use possible

*N.B. Another element could be the total revenues in the context of multiple indications for the same molecule owned by the same company

CF IN A NEW ERA, PERSPECTIVES

Jacquelien NOORDHOEK MA MSc, President CF Europe

Changing focus

Diagnosis: from sweat testing to DNA
Treatment: from symptoms to cause of CF
From national focus to international collaboration
Prognosis: from childhood to adults to elderly people with CF

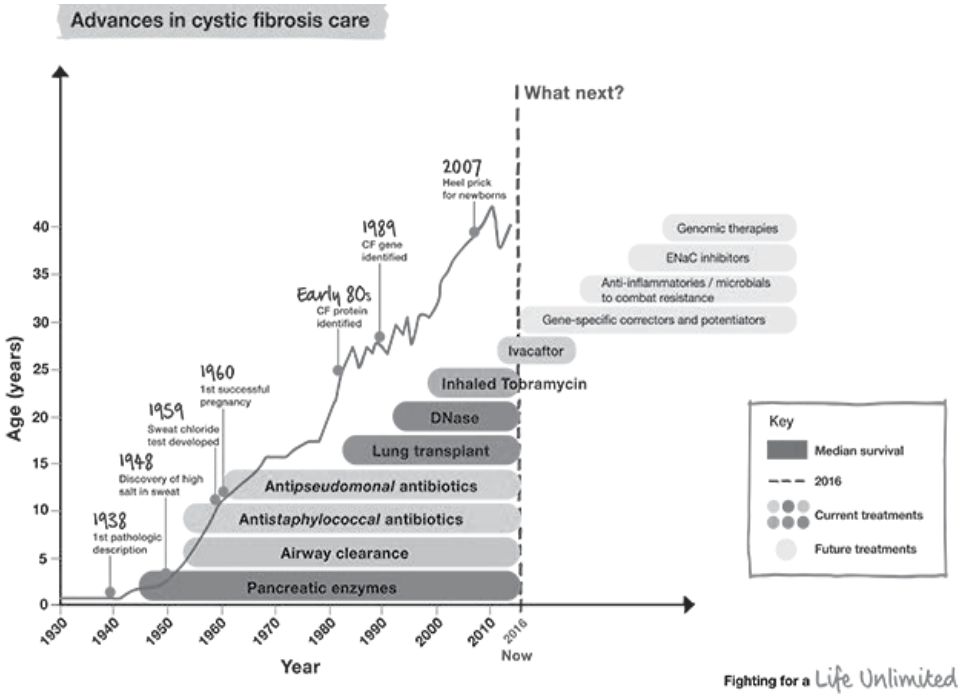
Diagnosis

DNA – mutations >2000 ; **www.CFTR2.org**

- Classification of severity
- Treatment opportunities !

Treatment

Symptoms: still important and improving !



Treatment of the cause of CF

Potentiators (Ivacaftor)
Correctors (Lumacaftor Tezacaftor Next gen)
Alternative strategies

Vertex, Galapagos, ProQr, Proteastasis, etc....
Bayer, Novartis, Boehringer, etc....

Ultimately: .....gene editing !

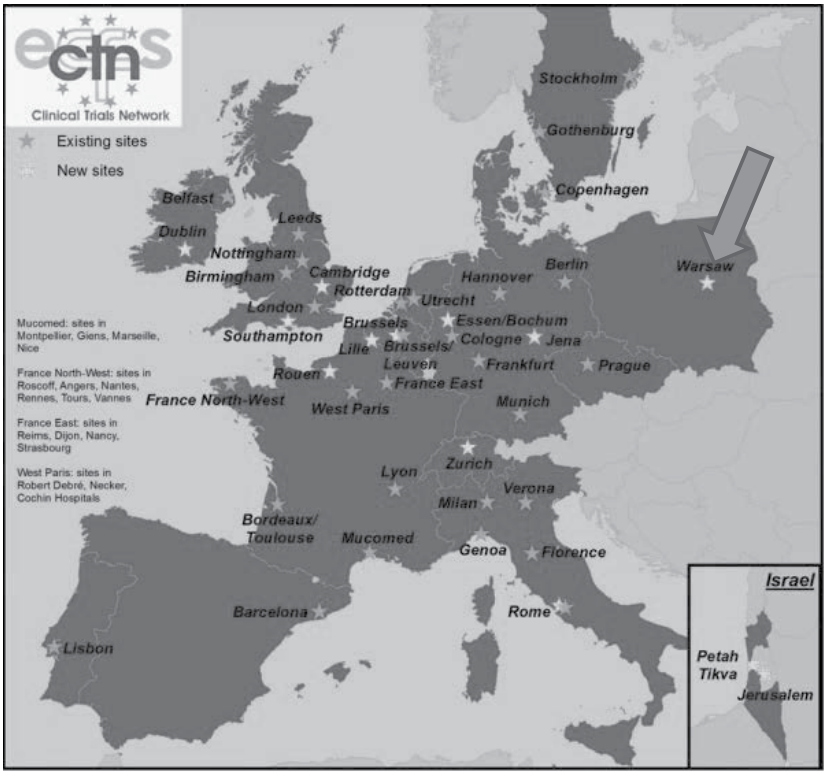
Treatment

ACCESS to new drugs !!!
National and international collaboration is necessary

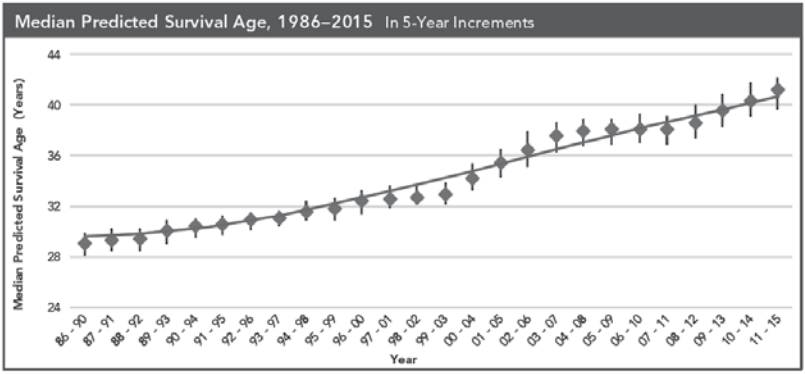
European Registry

31 Countries
>42,000 pts
17 National Registries
81 centers use ECFS Registry Software

ECFS Clinical Trial Network



Prognosis is improving and will improve faster!



Using the currently recommended method for calculation median predicted survival.

CFE in a nutshell

HIT CF Europe

- Will start in 2018
- People with ultra-rare CF mutations
- Biopsy : Miniguts (organoids)
- Testing of new drugs in miniguts
- Clinical trial via CTN (Warsaw)
- Reimbursement at European level
- Personalised medicine acces to drugs!
- **People from Eastern European countries might participate via ECFS-CTN centres in Prague and Warsaw**

STANDARDS OF CARE FOR CF PATIENTS: AN ECFS CONSENSUS DOCUMENT

Pavel DREVINEK
Department of Medical Microbiology & Prague CF Centre
2nd Faculty of Medicine, Charles University Motol University Hospital, PRAGUE, CZ

Concept of standards of care established in 2004

Journal of Cystic Fibrosis 4 (2005) 7–26

Standards of care for patients with cystic fibrosis: a European consensus

Eitan Kerem*, Steven Conway, Stuart Elborn, Harry Heijerman
For the Consensus Committee[1]
Department of Pediatrics and CF center, Mount Scopus, Jerusalem 91240, Israel

Visegrad Group V4 – CF conference 2008:
urging the politicians to allocate money and resources

" … the standards required **accord**
with the real possibility of achieving these standards
in different countries and different centres"

C. Castellani, Verona

April 2013, Verona

ELSEVIER

Journal of Cystic Fibrosis 13 (2014) S3 – S22

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Review

European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre

Steven Conway [a,*], Ian M. Balfour-Lynn [b], Karleen De Rijcke [c], Pavel Drevinek [d,e,f], Juliet Foweraker [g], Trudy Havermans [h], Harry Heijerman [i], Louise Lannefors [j], Anders Lindblad [k], Milan Macek [l,m], Sue Madge [n], Maeve Moran [o], Lisa Morrison [p], Alison Morton [q], Jacquelien Noordhoek [r], Dorota Sands [s], Anneke Vertommen [t], Daniel Peckham [u]

Journal of Cystic Fibrosis 13 (2014) S23 – S42

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Review

European Cystic Fibrosis Society Standards of Care: Best Practice guidelines

Alan R. Smyth [a,*], Scott C. Bell [b,c], Snezana Bojcin [d,v], Mandy Bryon [e], Alistair Duff [f], Patrick Flume [g], Nataliya Kashirskaya [h], Anne Munck [i,j], Felix Ratjen [k,l], Sarah Jane Schwarzenberg [m], Isabelle Sermet-Gaudelus [n,o,p], Kevin W. Southern [q], Giovanni Taccetti [r,s], Gerald Ullrich [t], Sue Wolfe [u]

Journal of Cystic Fibrosis 13 (2014) S43 – S59

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Review

European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis

Martin Stern [a,*], Dominique Pougheon Bertrand [b], Elisabetta Bignamini [c], Mary Corey [d], Birgit Dembski [e], Christopher H. Goss [f], Tanja Pressler [g], Gilles Rault [h], Laura Viviani [i], J. Stuart Elborn [j], Carlo Castellani [k]

Review
European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre

The centre

CF centre

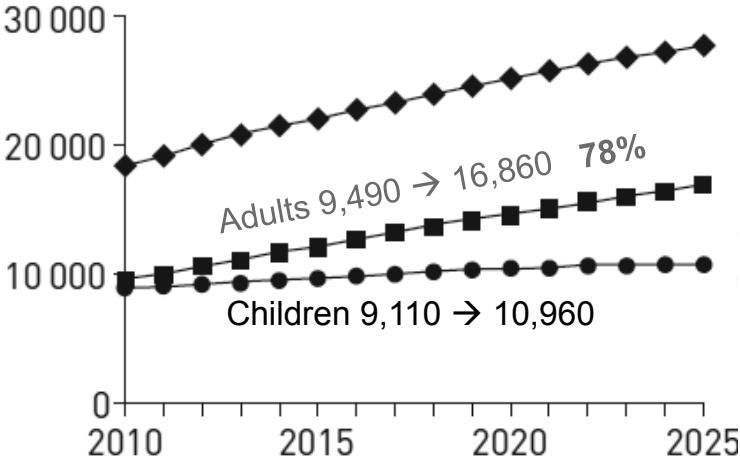
Minimal number of patients	• 100 (children or adults) • 50 acceptable in certain circumstances (centres with 50-100 pts linked to larger ones)
Paediatric and adult centres	• separate • adults to be in care of centres for adults • work closely together

- **access 24/7 by phone, for emergencies**
- **clear segregation policy**
- **sweat test laboratory**
- **appropriate microbiology service**
- **clinical research**

Report of the European Respiratory Society/European Cystic Fibrosis Society task force on the care of adults with cystic fibrosis

J. Stuart Elborn[1], Scott C. Bell[2], Susan L. Madge[3], Pierre-Regis Burgel[4], Carlo Castellani[5], Steven Conway[6], Karleen De Rijcke[7], Birgit Dembski[8], Pavel Drevinek[9], Harry G.M. Heijerman[10], J. Alistair Innes[11], Anders Lindblad[12], Bruce Marshall[13], Hanne V. Olesen[14], Andreas L. Reimann[15], Ampara Solé[16], Laura Viviani[17], Thomas O.F. Wagner[18], Tobias Welte[19] and Francesco Blasi[20]

B, CZ, DK, F, UK, NL



Review
European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre

MDT

Members	Notes to their role
respiratory paediatrician / pulmonologist	clinical lead
clinical nurse specialist	education, care, communication
specialist physiotherapist	inhalation therapy, airway clearance etc.
specialist dietitian	dietetic intervention
clinical microbiologist	infection control policy, antibiotic therapy
clinical psychologist	adherence, eating, anxiety, pain etc.
social worker	the gap between hospital and home life
clinical geneticist	diagnosis, genetic counselling
pharmacist	maximize the effect of therapies
database coordinator	epidemiology, benchmarking
secretary	administrative support

Review
European Cystic Fibrosis Society Standards of Care: Best Practice guidelines

Best practice

- Newborn screening
- Sweat test (>150 tests/year), CFTR analysis

- Screening for pancreas insufficiency (faecal elastase-1)
- Screening for allergic bronchopulmonary aspergillosis
- Screening for CF related diabetes (age of 10)
- Screening for bone mineral density (age of 8-10)
- Screening for non-tuberculous mycobacteria
- *P. aeruginosa* eradication therapy to start within 4 weeks
- *P. aeruginosa* exacerbation to treat with combination i.v. ATB for 14 days
- Mucus degradation with dornase alfa
- Hydrator therapy with hypertonic saline or mannitol

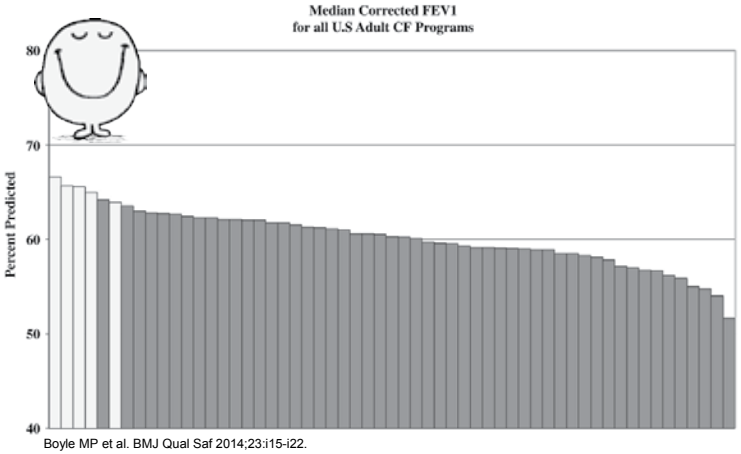
- Ivacaftor to patients with gating mutations
- Lumacaftor/ivacaftor as a treatment option to F508del/F508del patients

Submitted 2017: European Cystic Fibrosis Society Standards of Care: Best Practice Guidelines (Revised)

Review

European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis

Quality



Boyle MP et al. BMJ Qual Saf 2014;23:i15-i22.

- Median age
- Median age at death
- Proportion children / adults
- Median BMI
- Proportion of patients with LuTx
- Prevalence of chronic infections

12 Eastern Europe countries :

- **Existence of specialist CF centres (children)**

Yes	No
12	4

- **Size of the largest CF centre (children)**

< 50	3
50 -100	3
100 - 200	4
> 200	2

- **MDT composition**

respiratory paediatrician	12
clinical nurse specialist	8
specialist physiotherapist	11
specialist dietitian	10
clinical microbiologist	8
clinical psychologist	8
social worker	9
pharmacist	6
clinical geneticist	9
database coordinator	7
secretary	4

STANDARDS OF CF CARE IN V4 COUNTRIES
CZ, PL, SK, HU – PATIENTS PERSPECTIVES

ARELLANESOVÁ Anna, ZÁBRANSKÁ Simona, CZECH REPUBLIC
WOJTOWICZ Pawel, MARSZAŁEK Przemysław, POLAND
ŠTĚPÁNKOVÁ Katarína, SLOVAKIA
HÉCZEI Monika, MARSAL Géza, HUNGARY




A

1. Number of inhabitants in your country

	CZ	**PL**	**SK**	**HU**
	10,588,063	38 443 000	5,435,343	9,823 000

2. Number of registered CF patients

	CZ	PL	SK	HU
children	**345**	**1 017**	**131**	**278**
adults	**277**	**535**	**159**	**250**
total	**622**	**1 552**	**290**	**528**

PL - lack of the National Register, data from 2012
SK - Slovak National Registry 2014
HU - Hungarian national registry 2015

3. How many non-governmental CF organisations are there in your country? What is their mission? Is there any common platform or other form of cooperation?

CZ

There is only one NGO aiming to help patients with CF. The mission of the Czech Cystic Fibrosis Association is increasing the quality of life of Cystic Fibrosis patients and raising public awareness of this disorder.

PL

2 existing organizations over 25 years. On a nationwide scale and full spectrum of activity.
1 organization existing for 2 years. On local reach. Its main purpose is to support adult CF patients.
3 organizations at an early stage of development

2006 **Polish Society of Cystic Fibrosis** - was created from the transformation of the Polish Group. Working Cystic Fibrosis, which in 1992 was established at the Polish Society Pediatric. The founders of the Group were 40 scientists and doctors conducting research on cystic fibrosis. Currently PTM brings together about 80 members.

1987 **The Polish Society for Fighting Cystic Fibrosis** - the Society was established on the initiative of ordinary people who fight together for health and life for CF patients every day: doctors and parents of sick children. For more than 30 years, the Society has been representing and helping patients and their parents and is fighting to improve the cystic fibrosis treatment system in Poland.

1996 **Matio Foundation** - was founded in Krakow. The purpose of establishing the Foundation was to create an independent organization that everyone seriously experienced by fate could count on. And also, that patients with cystic fibrosis and their families should not be left alone with their own tragedy.

2015 **"Give them a Breath" Foundation** - the foundation is made up of parents and friends of Piotr Raczyński, who died in July 2015 for cystic fibrosis. The aim is to help people struggling with this deadly disease to support them not only materially, but also to bring comfort, understanding and share with ordinary human kindness.

3 organizations created a common platform for cooperation called **MukoCoalition**

Work together for Common goals to get Longer and better life

SK

1995 K**lub cystickej fibrózy**/ Klub rodičov a priateľov detí s cystickou fibrózou
- social field, lobby, financial support, parents/patients meetings.

2004 **Priatelia slaných detí**
- FR and beneficial activities, material support for CF families

2006 **Slovenská Asociácia Cystickej Fibrózy**
„Improvement of quality of life for individuals with cystic fibrosis and their family members."
- international activities and projects, education and CF conferences, publications, lobby,...

There is NO common platform. In the core issues we cooperate and speak „in one voice."

HU

Hungarian Association of Adults with Cystic Fibrosis (FCFBE)

Main objectives:
- to improve the length and the quality of life of every patient with CF in Hungary
- supports the adult patients and their families, specialized for their needs
- to encourage the CF patients to continously studying in high schools and universities
- to provide social support to find the proper job and to have successful carreer
- build and maintain the Hungarian CF Registry and provide the required reports and data for the professional needs
- collaboration with ECFS, ECFSPR and other international teams

Hungarian Cystic Fibrosis Association (OCFE) – since 1990

- Represents all the patients with CF across the country, but mainly children and their parents are involved
- Gathers information from various sources and informs those who may be concerned
- Supports patients in achieving the same quality of life as everyone else
- Raises awareness so patients will get more support from society and will experience less discrimination because of their illness
- Improves collaboration with CF health care teams and international organizations

4. How is your cooperation with CF Centers in your country?

CZ

We cooperate very closely with the largest CF centre in the Czech Republic (Prague) since we are located right next to it and then Brno but we plan to cooperate with all of them more closely in the future. We are part of the multidisciplinary team that takes care of CF patients right from the diagnosis and take them through life with CF. We communicate on a weekly basis to consult on how to help patients and what could our role be.

PL

- Cooperation is at a very good level.
- The organizations are participants in national scientific conferences. Representatives of CF centers actively support conferences and workshops organized by organizations.
- In CF centers, patients are informed about the possibility of using the help of the organization.
- Organizations actively support CF Centers (financing educational materials, funding medical equipment, loobing with the authorities to improve the treatment conditions for patients with CF)

SK

We have good cooperation with all CF centers, physicians and other health caregivers.

HU

Hungarian Association of Cystic Fibrosis Adults is trying to coordinate their work with the CF centers and communities, because we believe we could achive more together.
The Hungarian Cystic Fibrosis Association are in cooperation with the biggest childcare CF center and we are giving them active support.

5. How does your organisation communicate with central state authorities? How does your organisation communicate with municipal authorities (districts, cities and villages)?

CZ

The Czech Ministry of Health acknowledges the important role of patient organizations and therefore established Patient Council of the minister of health (12/2017) to communicate more and cooperate with patient representatives. Among other, this Council enables its members to comment on new legislative changes.
We cooperate with municipal authorities by applying for grants within their grant systems.

PL

1. We operate on a level
   national - ministries of health, education, social welfare.
   local - voivodships, local governments

2. We operate through
- individual initiatives, e.g. financing a specific cystic fibrosis drug
- under umbrella patient organizations (e.g. 'Citizens for Health', 'Strength in Genes')

SK
We have appropriate comunication with all state authorities, like Ministry of Health and Ministry of social affairs, insurance companies, districts.

HU
We are in comunication with the relevant state authorities, like Ministry of Health, National Health Insurance Fund and National Institute of Pharmacy and Nutrition.

B. HEALTH CARE SYSTEM

1. How many CF Centers are there in your country?
CZ
There are **5 CF centres** in the Czech Republic, they provide care for both children and adults - **Prague, Brno, Plzeň, Olomouc, Hradec Králové.**
At this moment, only Prague CF center joined the European Reference Network ERN-LUNG. None of the centers are however officially established by the Ministry of Health.

PL
There are **several "places"** where CF patients can get treatment. Most "places" specialize in a specific field (pulmonology, gastroenterology, etc.). They have various equipment and a number of isolated rooms. This requires frequent travel and movement for patients to obtain comprehensive treatment.
There are **4 leading CF Centers - Warsaw (Dziekanów Leśny), Rabka, Poznań, Gdańsk.**
There are **2 large centers for adults - Warsaw, Poznań.** Some adults are still treated in children's centers.
10 other centers are in Krakow, Katowice, Rzeszow, Lublin, Karpacz, Wroclaw, Szczecin, Bydgoszcz, Sosnowiec, Łódź

SK 3 for children, **3** for adults – **Bratislava, Banská Bystrica, Košice**

HU 15 centers – **13** for children, **3** for adults (1 center both),
but only 9 of these centers are registered ones.

2. What is the system of healthcare services for CF patients?
CZ
The healthcare in the Czech Republic is public, provided by the state in state hospitals.

PL
In Poland exist public health insurance for drugs and medical service covered by public health system. There is no national health care system/plan stricly for CF patients.
Of course, there is also a private sector where you can get help for a fee.

SK
Health care for CF is public, provided by the state in state hospitals. We have more healthcare insurance companies provided medicaments, equipments, ...

HU
We have public heath insurance, which covers the in- and outpatient care in the state hospitals.

3. Who provides the healthcare services ? CF Centers ? CF teams?
CZ
The healthcare is provided by CF specialists located in the CF Centers in state hospitals.

PL
Hospitals and state clinics (State healthcare system).

SK
Mainly the faculty hospitals, pulmonologists. We have no official definition for CF Center.
It is an ambulance of pulmonology where are reserved special hours for CF patients.
- It is usually a part of Children´s hospital,
- CF Centres for adults are part of TaRCH clinics for adults in faculty hospitals.
- There are no real CF teams and they have no special definition. No CF team meetings
- There are no members of CF teams and there are no responsibilities.
- Doctors, who treat CF, treat also other pulmonary and imuno-alergologic diseases, CF patients are a small proportion of their patients.
- CF nurse has workload officially for 1 CF Centre

Outpatient care:
– CF patients check-ups every 1 - 3 months in average
– Acute situations – at local doctor, some CF patients in CF centre as well
– Patients are sent to other specialists when it is required or within annual medical check-up by usual way (they have to make an appointment to each doctor and wait) and these specialists usually pay no particular attention to CF, they prepare a report, recommend medicaments, there is rarely direct communication between „CF doctor“ and other specialists
– home i.v. treatment (APAT) – it is rarely applied even though the Guidelines for HOME i.v. were approved in 2003 by our Ministery of Health and health insurance companies (un willingness of doctors to change the routines + complications with ATB and supplies).

Inpatient care - hospitalization:
– regular i.v. ATB treatment - every 3 months in average
– once a year, 3 – 5 days stay in hospital in order to carry out the annual examinations
– acute situations when required, complications
– CF patients stay very often in the same room with other patients, the rooms are in some CF centers without sanitary equipment
– presence of parents during hospitalization is well tolerated if they ask for it

HU
More or less established out and in-patient departments of hospitals provide regular care and check-ups and hospitalisations.
In the CF adult care there is only one CF center, there are a CF team takes care about the inpatients. Outpatiens have check-ups every 3 months.
In the CF childcare there is no CF center, CF in- and outpatient care usually in pulmonology departments, where are more or less educated pulmonologists takes care about the CF patients.

4. Are the medicaments free for CF ?

CZ

Yes, the medication needed to treat the symptoms of CF, such as enzymes, antibiotics and inhalation medication are fully subsidised.
As for Kalydeco, we have around 20 patients that are eligible for it. They receive it under a special regimen but the reimbursement has not yet been approved. The process has been dragging on for over 5 years...Orkambi is being administered to patients under so called compassionate use programme, for those who have lung function under 40% (FEV1).

PL

Most antibiotics are reimbursed. There is a flat fee of approx. EUR 0.85.
Tombramecyna is limited. Available as part of drug programs with high entry barriers.
Pulmozyme is reimbursed - flat fee 0.85 EUR / 30 pieces
Pancreatic enzymes - KREON 10,000 / 50pcs - not reimbursed. KREON 25,000 / 50pcs reimbursed 0,85 EUR (from 2018 price up to 2,9 EUR, LIPANCREA 16 000 / 60pcs - 2,5 EUR).
Nutrients - Fortimel MAX flat fee 0.85 EUR / 4 bottles 300ml to 18 years old. Full payment for adults.

SK

Most of the therapies, drugs and devices are free for CF patients are paid by health insurance companies.
Patient organization has lobbed a lot for free CF care 10 – 15 years ago – we got special EXCEPTION for diagnosis CF – the recepies have to be written by physisians in CF Centers:
- pancreatic enzymes
- antibiotics – p.o., i.v., inhalaed (+ TOBI)
- some mucolytics (+ Pulmozyme)
- all special drugs for CF
- nebulisers, physiotherapy devices
- nutritional supplements

HU

Free medication: Pulmozyme
inhaled antibiotics
enzyme substitution
inhaled Fluimucil
insulin
Fully covered: hospital treatment including iv. antibiotics
transplantation

Mostly covered: dietery supplements
for personal application Pari Boy SX nebuliser

5. If not, how much have to pay for them the patients?

CZ

Patients have to buy inhalators and their parts but they are partially reimbursed either by state or by CF Association.

PL

Average cost of home treatment, including refund medications (partly refunded) and supplements is 100-700 Euro/per month, dependent on age and condition of a patient.

SK
Still the CF patients have to pay many other drugs or services, but it is some way acceptable with social support from government.

30 – 50 EUR/month

All of these drugs have common use, so they are partially paid by other groups of patients. Some kind of inhalators (like E-Flow) and physio devices the patients have to buy.

HU
Average cost of home treatment, including medications (partly refunded) and supplements is 50-400 EUR/month, it depends on the condition of CF patient.
Some kind of inhalators (like E-Flow) and physio devices (chest vest) the patients have to buy.

6. Which medicaments, tools or therapies are not available in your country?
CZ
Some types of inhalators are not available. But can be bought abroad.

PL
None reimbursed for orphan drugs (Orkamibi and Kalydeco).
Lung transplantation - children (Vienna, Paris) is not reimbursed; Adults (Zabrze, Szczecin) is reimbursed.
Equipment for respiratory rehabilitation - 180 EUR / compressor; 35 EUR / nebulizer; 47 EUR / Pari PEP System, Flutter Pari O-PEP, Acapella, RC Cornet, etc. - the frequency of replacement results from the medical indications.

SK
- ORKAMBI and KALYDECO are not available in Slovakia
- Lung transplantations (Vienna, Prague) - not work very well
- In many cases there is the need to ask for exception – a lot of paper work (Pulmozyme, flutters, nutrition,...)

HU
CFTR modifying therapy is not available in Hungary

7. How is the chest physiotheraphy provided to CF patients?
CZ
Physiotherapy is taught at the beginning of treatment when newly diagnosed patients are educated about the treatment regimen. It is also done several times a day with in-patients in their rooms and patients have regular appointments with physiotherapists at their CF centre, at least once a year to work on their technique and incorporate new ones or according to individual needs.

PL
1. Parents after a child's diagnosis receive instruction on rehabilitation.
2. Every three months during check-ups - a physiotherapist should be consulted - but not in every center this is done due to the lack of funding for this service.
3. In the case of long hospital stays - the physiotherapist is normally available
4. A big problem is the lack of reimbursement for rehabilitation outside hospital stays. Patients have to pay extra for them.

5. Patient organizations organize training for parents and patients with physiotherapy.
6. Sometimes organizations also get grants for free home visits.

SK

- In every CF Center are physiotherapists trained in chest physiotherapy
- 2 weeks stays once a year with intensive physiotherapy is possible for CF children in sana tory in High Tatras – Dolný Smokovec
- Lack of communication between doctors, physiotherapists and patients
- CF Association organize every 1 – 2 years in cooperation with Physiotherapy society Chest physiotherapy courses

HU

The bigger centers (with >50 patients) could provide physiotherapy. Hospitals with smaller patiens number usually don't have well educated physiotherapists.

8. How does the nutrition counselling work?

CZ

Nutrition counselling is also provided at the beginning of treatment when patients are newly diagnosed. As part of the education programme, a newly diagnosed family meets a dietitian specialised for working with CF patients. The dietitian also reviews patient's food diaries and makes changes where necessary. These appointments are also regular, the dietitian checks in-patients, plus patients have the option of contacting the dietitian with questions or concerns.

PL

1. This area works quite well
2. Almost every visit there is a dietary consultation.
3. Patient organizations run infolines and workshops with the participation of dieticians.
4. There are several cookbooks with recipes especially for CF patients
5. A big problem is the lack of reimbursement of nutrients for adults
6. Home Enteral Nutrition (HEN) is available for CF patients

SK

In hospitals there is no nutrition counselling, NOT WORK correctly in all of the CF Centers in Slovakia.
CF Association printed „Book about nutrition for CF children and adults" in 2015.

HU

Some of the bigger centers have dieticians. But it is still the least represented part of CF care at the regional centers due to lack of financing . Thus nutritional councelling stays to be the responsibility of the already overburdened CF doctor.

9. Who edits the educational materials for CF community?

CZ

The Czech CF Association cooperates with CF specialists, such as doctors, nurses, psychologists and social workers on producing educational materials and they collaborate on editing on a regular basis.

PL Patient Organisation, Pharma Companies

SK Slovak CF Associations by cooperation with pharma companies.

HU The association edits them, the materials are in need of renewing.

10. Is the neonatal screening applied?

CZ Yes, since October 2009.
PL Yes, since October 2009. (1999 – pilot regional CF NBS)
SK Yes, since 2009.
HU No yet, but screening is planned to be introduced soon.

11. Have you succeeded in implementing European consensus about CF care standards into your healthcare system?

CZ

The new updated version of CF standards of care was translated into Czech. All the CF Centers still have gaps in implementing the Standards. The CF Association needs to work hand in hand with the hospitals to make sure the standards are fully adopted.

PL

"Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning." *Winston Churchill*

SK

Slovak Ministry of Health adopted on **20th of December 2010** document – recommendation:
„Odborné usmernenie MZ SR o poskytovaní zdravotnej starostlivosti
o pacienta s cystickou fibrózou"
Translation of ECFS document from 2004 adapted on the Slovak healthcare system and laws. Not fully accepted, it is only recommendation !
European up-dated version – 2014 ???

HU

European CF care standards have been adapted by the medical working group, its text was published. Hospitals are trying to incorporate the directions, but the financing is not resolved.

12. What would you need to change (priorities)?

CZ

Our priority is to **establish official CF centers recognized by the Ministry of Health**, so called Centers of highly specialized care for cystic fibrosis. We are working together with an umbrella organization, the Czech Association for Rare Diseases (ČAVO) to accomplish this goal.
A **benchmarking process** is being prepared (with the help of NCFS – the Dutch CF patient organization) to evaluate the level of care in CF Centers. We are very thankful for the support we receive from our Dutch friends.

PL

- **Improve care for adult CF patients. At least to be at the children's level**
- **Ambulatory care, home care (specifically antibiotic therapy)**
- **Implementation of national register**
- **Implementation CF care standards**
- **Access to new therapies and clinical trials**

SK

- **Access to new therapies and clinical trials**
- **Create the real CF Centers with real CF teams, where all members have defined real responsibilities with regular CF team meetings**
- **Implement the standards of care in the existing system - the government thinks that the recommended CF care is expensive**
- **Create better healthcare and social services for CF families**
- **There is a lack of profound motivation for young CF doctors**

HU

- In childcare there are too many hospitals - 12 taking care about CF children. Instead of that we should **establish maximum 3 - 4 well equipped CF centers with an educated CF teams**
- Approving the CF standards of care with the Ministry of Health
- Raising awareness
- Make strong partnership and cooperations with international organizations

C. SOCIAL FIELD

1. What are the possibilities to support your social system for CF patients and their families?

CZ

The system allows CF families to apply for "care allowance" for kids with CF from the age of 1 to 18 and there are 4 types, depending on the level of the child's special needs. There is a disability pension that patients can apply for from the age of 18 which also comes in 3 levels depending on the patient's level of disability. There are other various types of special case support, such as housing support, caring for a family member, paid sick leave and sometimes traveling costs. All of them are assessed on an individual basis.

PL

Cystic fibrosis is a disability disease - families with CF usually receive social support.
Social support for the caregiver : 350 EUR / month
Social pension for an adult : 165 - 200 EUR / month
Tax exemptions.

SK

Cystic Fibrosis is accepted as disability disease and CF families usually receive social support. Its voluntary not obligatory, complicate subjective administrative process.
- Social support for person giving care : 200 –300E/month
- Pension for disable adult person : 200 – 300E/month
- Nutrition (20 EUR/month)
- Hygiene
- Transport – travel cost
- Car – very rare

„Card for disabled persons" – some other advantages

HU
Providing training, information for the patients, parents, and for professionals, providing informational material about the illness for the parent/patient to forward it to teachers/employer/social worker, lobbying for medicaments and acts and regulations towards decision makers.
Both association have a new website and facebook groups where we can exchange ideas and help to each other.

2. Do you have any social workers? What are their responsibilities?
CZ
The CF Association used to have social workers and they used to be in charge of educating CF patients about their rights to claim allowance from the social system, how to apply for welfare, what are the types of welfare and where and how to get it. Now it is back to the hospital social worker due to a shortage of social workers in the association.

PL
There are social workers who are working within state and self-government units (social help for poor and disabled people) and in non-government organisations (including CF organisations). There are no state social workers dedicated strictly to CF patients.
Lack of proper training and qualifications of social workers,
Low social awareness about CF
Discrimination of CF patients - invisible disability
No possibility to combine work and social benefits - most often mothers leave work to take care of the child. But she could work remotely a few hours a day, but she can not.

SK NO
Klub CF for many years offered this service, but few years ago they stopped it (2003 – 2015).

HU
There are no dedicated social workers at the childcare, instead of that the parents can contact the Hungarian CF Association online.
At the adultcare there is only one social worker, who helps the CF patients eg. how to claim allowance, what are the types of welfare they are entitled and how they can get it.

3. Where are its weaknesses?
CZ
CF patients have to work hard sometimes to get support from the wellfare system due to loopholes in the legislation or lack of understanding of the medical assessment committee.

PL
Little funds, appropriate training and qualification of employees, low social awareness, too many responsibities are taken by CF organisations while part of it can be moved to social workers (state social workers with CF organisations together or more supporting state to NGO).

SK
- Discrimination of sick persons in many fields
- Low financial support for families and CF adults

- Discrimination of parents who decided to stay at home and take care about their sick CF children – in many levels – tax system, stop their professional growth, holidays, no social security,...

HU
Low financial support for families and CF adults.
Not transparent, continuously changing social system.

4. What would you need to change?
CZ
We need to **educate medical experts in the assessment commission** and help them understand **how much financial support from the social system CF patients really need** despite seeming "healthy" to the naked eye and help them understand that preventative care is necessary to keep patients alive and well so they can be equal members of society just like the healthy population and that it is simply not enough to just provide support in the late stages of the disease.

PL
The help of state for non government organisations or change and improvment of state service.

SK
- **Better definition of disabillity and needs of social support for CF families**
- **Social status of parents taking care about their CF children without discrimination**

HU
To achieve that CF patients and their families get a decent social support according to their disease. Make it more transparent, adaptable to new needs.

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Facebook group: https://www.facebook.com/cf.hungary

STANDARDS OF CF CARE IN UKRAINE - patients perspectives

VOLOSHINA Larysa, KIEV, UKRAINE
UPO - "Ukrainian Association of help for patients with cystic fibrosis"

1. Number of inhabitants in your country: 42 307 656

The population of Ukraine in 2017:

- In 2017, the population of Ukraine will decrease by 154 562 people and by the end of the year will be 42 307 656 people.
- Fertility: an average of 1,255 children per day (52.30 per hour)
- Mortality: an average of 1,779 people per day (74.11 per hour)
- 5% of the population of Ukraine has an orphan disease according to the data of the Ministry of Social Policy

2.Number of CF patients

Number of CF children: **615**
Number of CF adults: **212**
Total **827**

The number of patients with cystic fibrosis according the Charitable Funds in 2017

Regions	Children CF	Adult CF	Total CF	Charity funds by regions of Ukraine
Vinnitska	18	2	20	
Volynska	18	15	33	
Dnepropetrovska	65	29	94	
Donetska	9	13	22	
Zytomirska	16	8	24	
Zakarpatska	13	6	19	
Zaporizka	41	12	53	CF "Happy Child"
Ivano-Frankivska	27	7	34	
Kyivska	25	2	27	
Kirovogradska	15	10	25	
Luganska	5	3	8	
Lvivska	61	19	80	CF "Wings of Hope" CF"Devin"
Nikolaevska	12	3	15	
Odesska	48	12	60	CF "Life for you"
Poltavska	29	4	33	
Rivnenska	25	6	31	CF "Sentinel of Hope"
Sumska	12	0	12	
Ternopilska	21	2	23	
Harkivska	45	24	69	CF "Mukovystydoz" Association of parents of CF children with disabilities of patients
Hersonska	13	1	14	
Hmelnitska	19	6	25	CF "Breathe freely"
Cherkaska	18	10	28	
Chernovetska	7	3	10	
Chernigivska	9	3	12	
Kyiv	44	12	56	CF "Open palms" CF "I Hope and Believe"
Total	615	212	827	

3. How many non-governmental CF organisations are there in your country? What is their mission? Is there any common platform or other form of cooperation?

9 Charity funds for CF in Ukraine.

4. How is your cooperation with CF Centers in your country?
Cooperation is very weak. They communicate in case if there is a very complicated patient and they need a consultation from each other.

5. How does your organisation communicate with central state authorities? How does your organisation communicate with municipal authorities (districts, cities and villages)?
President of Association that represents the rights of the CF patient in Ukraine, actively participates in the MOH meetings, during which reimbursement list is formed for National programs, actively participates in tender and purchasing process. Due to the active participation MOH allowed regional leads of patient organization participate in the regional meetings.

B. HEALTH CARE SYSTEM

1. How many CF Centers are there in your country?
Officially: **4 CF Centers** have been registered throughout Ukraine; 2 Kiev, 1 - Lvov, 1 - Rivne (2 chambers).
Kyiv - "Center of Orphan Diseases" - KCCCH # 1 and Aleksandrovsky Adult Hospital.
Lviv - the Western Ukrainian specialized children's medical center, adults - are actively working on the creation of a center for adults.
Rivne - Chamber of children hospital, an adult ward.
Zaporizhzhia - the chamber of children.
Kharkiv - 2 chambers for children with CF, adults - in the stage of organizational issues.
Odessa is a children's regional hospital.
Dnipro - children's hospital and adults - pulmonary department.

2. What is the system of healthcare services for CF patients?
At the round table of 08.09.2017 at the Ministry of Health of Ukraine was discussed the question of including heads of areas in working groups in their places. An information letter was sent to all regions of the Ministry of Health - a list of heads of regions, representatives of individual units of the Association for the settlement of issues of program formation, financing, as well as all sorts of questions.
There are also regular meetings with the UNDP, MOH, DOS, DEAC and other organizations, as well as the Ukrainian Parliamentary Council on improving the situation regarding CF in all spectra.

Important normative documents:
Law of the Cabinet of Ministers of Ukraine on Orphan diseases
Article 53.1 (Ukrainian citizens with orphan diseases are continuously provided free of charge with necessary medicines, as well as products of special dietary nutrition. Effective from 01.01.2015)
Resolution of the Cabinet of Ministers of Ukraine # 160 dated March 31, 2015
Regional and Kiev city state administrations:
(In the 6th time, develop and approve measures to provide citizens with rare orphan diseases, medicines and necessary special dietary nutrition that are bought for the money of local bud-

gets. Provide the costs of financing these activities with the calculation of financial capacity of the budgets. April 15, 2015)

Order of the Ministry of Health No. 1422 dated 29.12.2016. the introduction of amendments to the order number 751 dated 09/28/2012.

(when forming the nomenclature, the doctors included in the working groups of experts have the full right to be guided by all approved international unified clinical decisions, as well as the protocols of treatment taking on the basis of the necessary information).

Order of the Ministry of Health 1303 dated August 17, 1998

(On introduction of free and preferential delivery of medicines by prescriptions of doctors in the case of ambulatory treatment of certain population groups.)

Order of the Ministry of Health # 360 of July 19, 2005

(Instructions on how to prescribe, preserve and destroy prescription forms.)

3. Who provides the healthcare services ? CF Centers ? CF teams?

Provision of assistance for CF:

Genetic is the main physician, a multidisciplinary teams are formed in part in Kyiv and Lviv in the centers for children

4. Are the medicaments free for CF ?

Throughout Ukraine, the provision of drugs is completely different and conditions of stay in the hospital as well. We cannot fail to say about such **regions, where there are no programs, there is practically no financing**, no conditions for obtaining adequate consultation. Parents are forced to turn to existing centers, which entails unforeseen expenses. Often expenses exceed revenues.

Budget of the Ministry of Health of Ukraine for 2015 - 2018:

Children:

2015 (590 children) - 8000,0 thousand UAH

- Pancreatin 10000
- Pancreatin 25,000

2016 (597days) - 32 227.82 ths. UAH

- Pancreatin 10000
- Pancreatin 25,000
- Dornase Alpha

2017 (615 children) - 65 810,1 thousand UAH.

- Pancreatin 10000
- Pancreatin 25,000
- Dornase Alpha
- Colistomethate of sodium

Total 100% need for basic treatment of children with cystic fibrosis in 2018 - 198 677, 98 thousand UAH

- Pancreatin 10000
- Pancreatin 25,000
- Dornase Alpha
- Colistomethate of sodium
- Tobromicin is inhaled
- Ursodeoxycholic acid

Adult:
"Centralized procurement of medicines for the treatment of adult patients with CF"
Approximately 100% of the need for data from the registry of patients on MW is 35 948, 8 thousand UAH. Approved adult provision for 2017 (212 people) 89.16% of enzymatic therapy - 11000.0 ths.
- Pancreatin 25,000

The total 100% need for providing basic therapy for adults with cystic fibrosis older than 18 years old (217 people), by 2018 will amount to 135,916,107 thousand. UAH
- Pancreatin 25,000
- Dornase Alpha
- Colistomethate of sodium
- Tobromicin is inhaled
- Ursodeoxycholic acid

5. If not, how much have to pay for them the patients?
For kids - 25 thousand USD per year to treat OOP
For adults - 38 thousand USD per year to treat OOP

6. Which medicaments or tools are not available in your country?
Concerning medicines: if we speak in general, namely, for the whole of Ukraine, clearly with full certainty, I state that the drugs are precisely antibiotics for inhalation, and more specifically: tobramycin inhalation, Tobi Podhaler, colistin, mucoclear, fluimucil with antibiotic; Cloxacillin, Flufloxacillin, Fucidinium Tablet Form is absent, as well as vitamins for CF are not available.
The physiotherapy devices - breathing simulators in any of their performance for Ukraine are not available, including the belt for physiotherapy.

7. How is the chest physiotheraphy provided to CF patients?
In Kiev CF center, physiotherpist come for excercises to the patient and they do individual set of exercises. In Lviv CF center patients go to physiotherapist and also do individual set of exercises according to the patients feeling

8. How does the nutrition counselling work?
This is under development. Doctor in Kiev CF center is going through additional education and trainings. Education in regions is also beeing done.

9. Who edits the educational materials for CF community?
None, negotiations are being held

10. Is the neonatal screening applied?
The screening was conducted in a centralized manner throughout the territory of Ukraine from **2011 to 2014**. Screening was stopped in 2014 due to the lack of financing. At the moment, the process has been restored, namely applications are collected from all regions. **In may 2018** the screeting program will start againg all over Ukraine due to the National funding program.

11. Have you succeeded in implementing European consensus about CF care standards into your healthcare system?
European consensus was the core document to create the **National protocols of CF treatment in Ukraine.**

12. What would you need to change (priorities)?

- **Creating a registry throughout Ukraine**
- **Reference Centers**
- **CF Centers**
- **The opportunity to receive free consultation, examination, inpatient treatment without reference to the place of residence**
- **Expansion of nomenclatures**
- **Increased funding for regional, provincial, city programs**
- **100% of the provision of vital drugs in full**
- **Consideration of re-liberation for CF?**

C. SOCIAL FIELD

Children with CF - often parents are faced with the problem of not accepting children in kindergartens, have to prove, explain that for the disease cystic fibrosis, ask that in time they give enzymes in the kindergartens.
Adults with CF, due to the fact that the question of providing adult patients has not been raised for a long time, often adults are not ready to tell what they are, they hide their specificity and their needs in educational enviroments and at work.
Families, employees! It is not ready until Ukraine provides in full the necessary social assistance to families where there is a child with a rare disease.

1. What are the possibilities to support your social system for CF patients and their families?
None

2. Do you have any social workers? What are their responsibilities?
Social workers do exist, but they do not provide any support to the families with CF kids.

3. Where are its weaknesses?
There are no programs of CF families support

4. What would you need to change?
Approval in parliament and implementation of national program of social support for CF families.
The branch of social assistance and support needs to be developed.
Mentality.

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"We are all just people.
But for parents, we are the meaning of life, for friends - kindred spirits,
for the loved ones - the whole world !"

STANDARDS OF CF CARE IN LATVIA - patients perspectives

BELLINSKA Alla, KOLESNIKOVS Sergejs, CF patients assotiation, LATVIA

Unfortunately this year is very busy with many events at the same time. Last week we provided international education 2 day conference for Latvian doctors and patients. Next week round table meeting will take place with the government about transplantation problems in Latvia. Due to this reason I am not able to be with you. In my mind I think and support your conference and all topics will be discussed. On behalf of me and Latvian CF organization Mr. Sergejs Kolesnikovs will give a presentation and will represent our organization. Wish you success, let's keep in touch.

Sincerely Yours – Alla

1. Number of inhabitants in your country: 1 933 200

2. Number of registered CF patients

Number of CF children: **30**

Number of CF adults: **14**

3. How many non-governmental CF organisations are there in your country? What is their mission? Is there any common platform or other form of cooperation?

CF patients assotiation

- Mission: develope and improve CF patients quality of life
- Fight for appropriate care and treatment for patients/children with CF
- Get governmental attention to problem of CF

Latvijas Reto Slimību Alianse (platform for cooperation with other rare diseases associations)
- Created in October 2014, merging 5 other associations, CF association included.
- Mission: develope and assure cooperation among rare diseases associations in Latvia and outside
- Develope awareness of rare diseases problems in society

4. How is your cooperation with CF Centers in your country?
Currently in the Children`s Clinical University Hospital is created a **CF consulting-room**. Latvian CF association cooperate with this clinical CF specialists, doctors and hospital management.

5. How does your organisation communicate with central state authorities? How does your organisation communicate with municipal authorities (districts, cities and villages)?
- Within last 4 years LCF association organized International conferences where doctors, patients, relatives and society were educated about different issues CF patients meet.
- In 2016 conference lectures were recorded and placed into portal for education of Latvian doctors. As result all Latvian doctors got aproach and educated about CF actualities.
- In 2015 CF assotiation gave an influence on the Cabinet of Ministers regulations and got a special budget for Food for Special Medical Purposes. After 2015 FSMP products for CF patients are prescribed for free according to the budget and delivered directly to patients home in any place of Latvia.
- The association actively participates in meetings and discussions on guidelines for rare diseases and the necessary changes to improve the patient's situation.
- 30 september 2016 within III International CF conference a round table discussion were organized for EU experts and Latvian doctors, and government representatives about such topics:
    - newborn Screening necessity and its implementation in Latvia
    - discussions on possibility to include new generation medications for CF treatment (CF genes mutation correctors)
- LCF association participated in decision making and got positive move ahead Pulmonal transplantation availability in Latvia. State declared that from 2018 Pulmonal transplanta tions will be available and budgeted.
- In 2017 LCF association prepared and applied their proposals for Rare diseases plan for period 2017 - 2020, which is very important document, as it will set up finances and priori ties.
- Currently LCF association prepare round table discussion about donor organs availability in Latvia in Children's Clinical University Hospital on 24 November 2017. There is a ne cessity to do changes in legislation which would allow to increase the amount of potential donors. Currently there are a lot of restrictions.

B. HEALTH CARE SYSTEM

1. How many CF Centers are there in your country?
- Currently CF patient count is under <50, it does not allow to have a special centre.
- Currently in the Children`s Clinical University Hospital is created a CF consulting-room, where a team of specialists is giving service to CF patients. It is an additional work for specialists among other duties in hospital.

- The Government of Latvia plans to create RARE disease centre in the Children`s Clinical University Hospital in Riga.

2. + 3. What is the system of healthcare services for CF patients? Who provides the healthcare services ? CF Centers ? CF teams?

CF patients receive the same care as all people in Latvia and additionally CF patients receive care in **CF cabinet**. That means – patients are examined at Cabinet, on average, 4 times a year (by pulmonologist, physiotherapist, nutritionist, if necessary – by gastroenterologist, otolaryngologist, psychologist or others), once a year they have yearly control at day care unit, they receive medicine (free of charge) and prescription (free) and direction to general practitioner.

4. Are the medicaments free for CF ?

- Medicine for CF treatment is free of charge – medicine for regular treatment and for treat ment of exacerbation. General practitioners are available by the place of residence.
- Untill age of 18 patients receive prescribed medicine (special food included) in Children`s Hospital where CF consulting-room is located. Children`s Hospital have special budget for CF patients treatment. General practitioners are also available by request.

5. If not, how much have to pay for them the patients?

Kreon 10 000 Latvia is for free a special budget for CF patient, but 100 % offset Pangrol 25 000. Who wants to use 25 000 Kreon it's available, but have to pay themselves 10% of the amount. Pulmozyme is available, but not for every day.

6. Which medicaments or tools are not available in your country?

In Latvia we do not have Ivacaftor (we did not have patients with treatable mutations) and Orkambi (we have patients homozygots for delF508, but the price of medicine is unavailable).

7. How is the chest physiotheraphy provided to CF patients?

- Chest physiotherapy is provided by patients themselves and their parents – they are trained by special physiotherapist. In Riga and some bigger towns it is possible to attend physiotherapist for activities twice a year for 10 days – free.
- In cooperation with the Latvian National Rehabilitation centre "Vaivari" team of doctors and Lithuanian CF asociacion was organized expierence exchange trip to Lithuanian rehabilitation centre "Abromiškes", 2015
- Discussions followed about necessity of rehabilitation for CF patients. Since 2016 all CF patients untill the age of 18 with a doctor`s prescription can get a rehabilitation course for free in the mentioned centre.

8. How does the nutrition counselling work?

In CF centre there is a nutritionist, she analyses patients everyday.

9. Who edits the educational materials for CF community?

- CF cabinet of doctors has prepared materials for CF patients about physiotheraphy, desin fection of inhalators, and just now – about food.
- If new CF patient discovered – CF team specialists educate patient and relatives about basic treatment priorities: physiotherapy, inhalation technics, food and medicine intake.
- LCF association helps to patients, relatives and also doctors in all life situations.

10. Is the neonatal screening applied?
We do not have newborn screening in Latvia.
In 2017 LCF association participated on meeting with the Ministry of Health and made proposals for State Mother and Baby Health Plan 2018 - 2020. In this plan newborn screening budget and plan for implementation starting from 2018 second half is also included.

11. Have you succeeded in implementing European consensus about CF care standards into your healthcare system?
Consensus about CF care standards is translated in 2012 and since than accepted by Children`s Hospital and doctors associations.
According to budget oportunities doctors and hospitals try to apply them in everyday work and treatment.
On State level the main stream is to implement Rare diseases treatment according to EU guidelines.

12. What would you need to change (priorities)?

- **It is necessary to release adult CF patients after the age of 18 from co-pay in the hospital. Rehabilitation for adult patients in Latvia is not free. Is necessary Provide care at home for CF patients.**
- **Vitamin D and some other necessary analyzes for all patients need pay themselves. It is in the hands of the patients, that's way many patients do not make the necessary analyzes.**
- **There is not enough control.**
- **Enzymes need to be improved, calculated and controlled in patients.**

C. SOCIAL FIELD

1. What are the possibilities to support your social system for CF patients and their families?

- Children with CF diagnose have rights to getting disability status for term from 2 to 5 years. After ending this period they passing special disability specialists commission and get again status. Parents who take care of a child with disability status get monthly 150 EUR.
- After age of 18 years patients with CF diagnose get 2nd or 3rd level disability status.
- In severe cases 1st level disability status can also be applied. For such patients there is possible to get oxygen therapy.
- In 2015 LCF fighted for oxygen therapy availability for CF patients and palliative care patients. From that period Children`s Hospital have movable oxygen equipment.
- Adults with disability 1st level are geting 83,24 EUR monthly. But patients who are disable 1st level since childhood receive 138,74 EUR
- Adults with disability 2nd level are geting 76,84 EUR monthly. But patients who are dis able 2nd level since childhood receive 128,06 EUR
- Adults with disability 3rd level are geting 64,03 EUR monthly. But patients who are disable 2nd level since childhood receive 106,72 EUR
- 1st level disabled persons are free from payments in Hospital. **All CF patients after age of 18 years have to pay for treatment in hospitals and pay also for each visit to doctor** (stationary day in hospital around 10 Eur, operations and manipulations costs according to price

list, each visit to specialist around 5 Eur, to general practitioner - 1,40 Eur)

- LCF association have cooperation with the largest charity organisation in Latvia "Ziedot.lv" already for 4 years and they help to pay treatment charges.

2. Do you have any social workers? What are their responsibilities?

A social worker is available in local governments depending on the patient's social status.

3. Where are its weaknesses?

There is not enough support from social workers in the country for CF patients. They also do not have enough knowledge about CF patient care. Social workers are available to CF patients after their residency at municipal social services and may only be requested by a disabled person in group I or a palliative care child.

4. What would you need to change?

It is necessary to change the legislation of Latvia for the provision of social worker assistance to CF patients, because the CF patient does not receive special social guarantees.

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STANDARDS OF CF CARE IN LITHUANIA - patients perspectives

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RADZIUNIENE Violeta, Pediatric Pulmonologist
Cystic Fibrosis Centre, Vilnius City Clinical Hospital, VILNIUS, LITHUANIA

1. Number of inhabitants in your country: 2 812 713

2. Number of registered CF patients

Number of CF children: **32**
Number of CF adults: **44**

3. How many non-governmental CF organisations are there in your country? What is their mission? Is there any common platform or other form of cooperation?

There is only one non-governmental CF organization in Lithuania - CF Association.There is webpage of this association with all information for patients.

1994 **Lithuanian CF Association**

- to connect all who care about CF in Lithuania
- to represent patients, parents and medical staff in different goverment's, law and others institutions
- to defend there interests as much as possible

4. How is your cooperation with CF Centers in your country?
It depends from what side do you discuss about cooperation. If we talk about it from association side, the head of association contacts very often with centre's medical staff, it is ussualy practice. From other side, as a doctors, we solve many different problems with CF association, helping to reach not only medical and social questions, but sometimes political questions too.

5. How does your organisation communicate with central state authorities? How does your organisation communicate with municipal authorities (districts, cities and villages)?
- Lijana Kazlauskiene is a member of Council of representatives of patients' organisations of Lithuania
- She is an active member of different work groups in Ministry of Health of The Republic of Lithuania
- Active discussion with National Health Insurance Fund

B. HEALTH CARE SYSTEM

1. How many CF Centers are there in your country?
Cystic Fibrosis care in 2 hospitals - for both - chlidren and adults:
Vilnius - City Clinical Hospital
adult care since 2015
Kaunas - Clinic at the Lithuanian University of Health Science
adult care since 2012

2. What is the system of healthcare services for CF patients?
The National Health Insurance Fund (NHIF):
all patients covered with the compulsory health insurance (CHI) can receive all required services in health care institutions located in Lithuania free of charge. Payments for all these services are made from the means of the budget of Compulsory Health Insurance Fund for health care institutions, which have entered into the agreements with the Fund.

3. Who provides the healthcare services ? CF Centers ? CF teams?
CF teams in CFcentres. Sometimes - GP, but usually GP or parents call to CF centre, if they have a problems.

4. Are the medicaments free for CF ?
Medicaments for outpatients (free, but it depends from annualy/quartelly political decisions): List A: Cystic fibrosis (100% free):
Amikacinum, Cefoperazonum, Ceftazidimum, Tobramycinum, Azitromycinum, Cefuroximum, Ciprofloxacinum, Clarithromycinum, Pancreatinum, Dornasum alfa Salbutamolum
For inpatient - free

5. If not, how much have to pay for them the patients?
The Ministery of Health called it 100% free, but they compensate only base price patient needs pay additional money and from NOV 2017 it is extra payment, especially for Creon, Amoksiklav, Azitromycin (especially for adults patient).

6. Which medicaments or tools are not available in your country?
We have all medicaments and tools.

7. How is the chest physiotheraphy provided to CF patients?
Medical rehabilitation for adult patients is prescribed by their physician, based on recommendations of physician of physical medicine and rehabilitation and for children – by a physician of physical medicine and rehabilitation 14 - 22 days 1 - 2 times /year (as needed)
Chest physiotherapy: exercises min 2 times /day, Vest, Acapella

8. How does the nutrition counselling work?
European consensus, Brompton Royal Hospital recommendations
Dietician: outpatient - as needed (min 1/year), inpatient - always

9. Who edits the educational materials for CF community?
CF Association and CF doctors edit educational materials for CF families - usually 1 - 2 times/year.

10. Is the neonatal screening applied?
There is no neonatal screening for CF yet.

11. Have you succeeded in implementing European consensus about CF care standards into your healthcare system?
Yes, we have

12. What would you need to change (priorities)?
1. The compensation of medicaments must be totally 100%, without any additional pay ment, which are not anticipate every 3 months due to new political trends/opinions/ points in our country.
2. The inhalators, vitamins are not in compensation list.

C. SOCIAL FIELD

1. What are the possibilities to support your social system for CF patients and their families?
As it is now, it works.

2. Do you have any social workers? What are their responsibilities?
There are social workers at CF centres. CF association members and doctors work with local social worker in certain situations, for example:
- assist families with social issues
- assist with nutrition at school
- assist with dissability allowance

3. Where are its weaknesses?
There are little contact without CF centres teams and local social workers due to responsibilities. There are no one special social system in Lithuania for such diseases like CF

4. What would you need to change?
To initiate to create such general system (start with Ministries of Health and Social Security and Labor)

CONTACT:
www.cistinefibroze.lt

STANDARDS OF CARE FOR CF PATIENTS IN CZECH REPUBLIC

SKALICKÁ Veronika, M.D.
Prague CF Centre, 2nd Medical School of Charles University and Motol University Hospital, PRAGUE, CZECH REPUBLIC

Country	**CZECH REPUBLIC**
Population	**10 588 063**
Number of CF children	**330** (18 y + 364 d)
Number of CF Centers for children	**5**
Number of CF adults	**292** (from 19 y)
Number of CF Centers for adults	**5**
Number of CFTR-related disorders patients:	
CFTR-RD or atypic CF	**30**
CF-SPID	**32**

1.How is CF care organized in your country: CF Center – CF team - Other specialists – what is their role in the system of care for CF patients in your country?

As for November 2017, in total 622 patients with cystic fibrosis (CF) were registered in five CF centres in the Czech Republic. Centres are not oficially recognised by Czech authorities. The largest CF centre (taking care of 179 paediatric and 155 adult CF patients) is the Prague one; remaining centres are located in towns of Hradec Kralove (55 pts), Brno (120 pts), Olomouc (60 pts) and Plzen (50 pts). Although four latter CF centres belong to teaching hospitals which play a pivotal role in health care of the respective regions and are authorized to act as CF centres by the Ministry of Health, neither of them meet all criteria for a CF centre defined by the ECFS document. Besides the borderline number of patients (recommended to be over 50; and this is the case only of Hradec Kralove and Brno CF centres where the number is around 55), they do also have staffing problems.

The only CF centre left which fulfils all necessary requirements for a CF centre proposed by ECFS standards (including the number of patients and a functional multidisciplinary team) is a joint centre for CF children and adults in Prague.

Since the centre cares for both children and adults, it is being managed from Paediatric as well as Internal Departments, and also co-managed by the Genetic Department. The service provided by the centre ranges from the CF diagnostics (i.e., sweat tests, CFTR allele detection, and nationwide neonatal screening) to conventional CF care (e.g., standard follow-up visits every three months) and CF specific therapy (i.e., airway clearance, nutritional support and infection treatment). We pay particular attention to the infection control issue as many of our patients became infected with a transmissible strain of Burkholderia cenocepacia in the past. Patients are segregated according to their microbiological status and kept apart from each other to prevent further spread of the infection.

- Dpt. of Paediatrics
  In-patient and out-patient dpt.
  (care for children)
- Dpt. of Pneumology
  In-patient and out-patient dpt. (care for adults)
- Dpt. of Rehabilitation
  Physiotherapy consultations
- Dpt. of Biology and Medical Genetics
  Genetic counselling, molecular diagnostics

Cooperation with: Clinical psychology, Social dpt., Gastroneterology, Diabetology and Endocrinology, Nutrition advisory, ENT, Transplant team, Kardiology, Nephrology, Obstetrics and gynecology etc.....

Laboratory and commmon examination background: sweat testing, spirometry, anthropometry, microbiology, radiology - CT ....

A core team in the Prague CF Centre consists of following members who are all experienced in CF:

pulmonologists (3 for children + 2 for adults)
specialist nurses (1 + 1)
physiotherapists (2 + 1)
gastroenterologist
diabetologist
geneticists (2)
psychologist
dietician
social worker
anthropometrist

To secure the highest possible quality and the most comprehensive care, the centre is in close contact with other departments such as microbiology, immunology, ENT or Transplant centre.

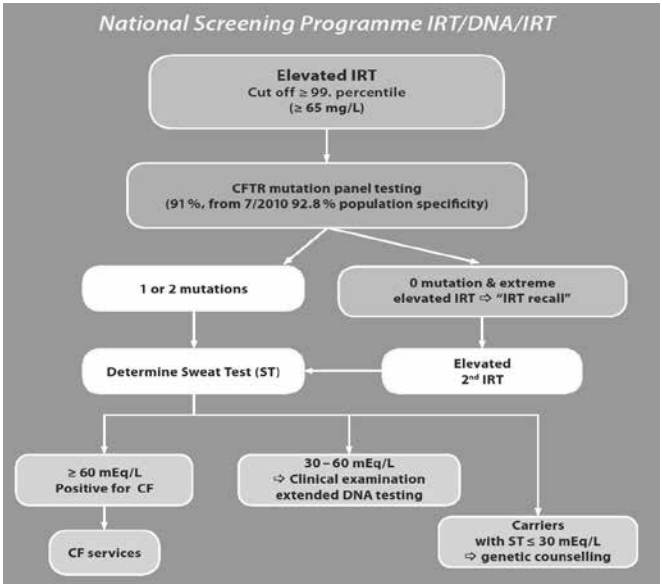
Physician (paediatrician, pneumologist)
Clinical psychologist
Specialised nurses
Physiotherapist
Nutritionist
Microbiologist
Geneticist
Social worker
Patients organisation „CF Club“ coordinator
Registy datamanager

2.Therapy: who pays the medicines and necessary equipments, transplantations, new therapies,....? How is the care paid, expensive therapie, orphan drugs? Insurance/patients ? How physiotherapy is performed? At home, in the hospital, out-patient ?
Essenatially, the care is fully covered by national health system. However, some devices (e.g., Flutter) are paid by patients who may apply for partial reimbursement from the patient's organization.

Medicines and necessary equipments covered mostly by
- insurance
- extra charges (minor part) borned by patients : nebulizers, airway clearance devices, vitamines, sipping

Transplantations: fully by insurance
New expensive therapies: fully by insurance by special law when only way of treatment (subject to special approval provided by insurance company)

3. Is the neonatal screening performed in your country?
Neonatal screening was launched in spring 2009.



4. Does actual National CF Registry exist in your country?

Czech Registry of Cystic Fibrosis :

- Whole population of Czech CF patients registered
- Collecting clinical and demographic data from consenting CF patients
- Data used to measure and evaluate aspects of CF and its treatment
- The Czech Registry of Cystic Fibrosis is part of The ECFS Patient Registry
- All Czech CF centres are encouraged to participate in entering data into an existing national CF registry (www.cfregistr.cz). Its goal is to collect relevant data on all live Czech CF patients, to update it on a regular basis and to make the registry compatible with the European database.

5. Do you have access to new therapies? Have you done some CF Clinical trials?

Number of patients treated with **Kalydeco: 16** – by insurance
Number of patients treated with **Orkambi: 18** – by donation (patients after turnout in clinical trials, patients in critical condition)

CF Clinical trials: Prague center - member of ECFS CTN
Number of CF Clinical trials conducted at Prague CF center during the last 3 years:
1x (phase III / adults and children), 2x (phase II / adults), 1x (phase II / adults and children), 2x (phase Ib study / adults)

6.How you cooperate with national patients organisations? What do you expect from them ?

„CF Club“
One member of CF medical team is a member of CF Club committee
A member of professional Club staff regularly joins CF team

7. What you feel are the main problems in CF care in your country?

Registration and financing „new therapies“

STANDARDS OF CARE FOR CF PATIENTS IN SLOVAKIA

FEKETEOVÁ Anna, M.D.
CF Center, Children´s Faculty Hospital KOŠICE, SLOVAKIA

Country	**SLOVAKIA**	
Population	**5 435 343**	(31.12.2016)
Number of CF children	**131**	
Number of CF Centers for children	**3**	
Number of CF adults	**159**	
Number of CF Centers for adults	**3**	

ECFS PR 2014

Number of CFTR-related disorders patients: **129**

1.How is CF care organized in your country: CF Center – CF team - Other specialists – what is their role in the system of care for CF patients in your country?

We have official CF Centers: 3 for children, 3 for adults:

Bratislava, Banská Bystrica, Košice

- It is usually an ambulance of pulmonology where are reserved special hours for CF patients.
- CF centre for childern is usually a part of Children´s Faculty hospitals
- CF Centres for adults are part of TaRCH clinic for adults in faculty hospitals.
- There are no real CF teams and they have no special definition. CF teams do not exist, there is no working time for CF, so therefore there are no CF team meetings.

- There are no members of CF teams and there are no responsibilities
- Doctors, who treat CF, treat also other pulmonary and imunoalergologic diseases, CF patients are a small proportion of their patients (about 10%) - they can prescribe the special CF medicines
- CF patients are cured by doctor - pulmonologist, in one ambulance it is doctor imunoalergologist.
- Patients can regularly see physiotherapists in many hospitals in Slovakia, but it is not tracked systematically.
- In most hospitals there is NO nutrition counselling.
- There isn't provided psychological support to CF families.
- A CF nurse has workload officially only in some CF Centre.

Outpatient care - ambulance care:
- CF patients check-ups every 3 months in average (every month if it is necessary)
- once a year the annual examinations
- acute situations – at local doctor, some CF patients in CF Centres as well
- home i.v. treatment (APAT) – it is rarely applied with some children, with adults almost never - even though it is approved by Ministry of Health and health insurance companies (the main reason is unwillingness of doctors to change routines).

Inpatient care - hospitalization:
- regular ATB cures – no
- acute situations when required, complications
- CF patients sometimes, but not very often are in the same room with other patients
- the rooms are without sanitary equipment in some CF Centers
- presence of parents during hospitalization is recommended by doctors

Other specialists have no exact role, they work as specialists for other patients too, ussually according the recommendation of CF doctor.
Patients are sent to other specialists when it is required or within annual medical check-up by usual way (they have to make an appointment to each doctor and wait) and these specialists usually pay no particular attention to CF, they prepare a report, recommend medicaments, here is direct communication between „CF doctor" and other specialists.

2.Therapy: who pays the medicines and necessary equipments, transplantations, new therapies,....? How is the care paid, expensive therapie, orphan drugs? Insurance/patients ? How physiotherapy is performed? At home, in the hospital, out-patient ?

- Therapies, medicines and equipments are paid by health insurance companies.
- Patient organization has lobbed exception, so the insurance companies fully pay the pancreatic enzymes, ATBs, some mucolytics for CF patients.
- Pulmozyme, TOBI and nutritional supplements are fully covered as well.
- The nebulizer PARI and some physio equipments (e.g. flutter, PEP masks,...) are fully covered, but no eFlow
- In some cases there is the need to ask for exception.
- Once a year CF children can have 2 weeks physiotherapy stay in sanatory in High Tatras (Dolný Smokovec)
- Lung transplantations possible in Prague and Vienna - until 2016 - 9 CF patients

3. Is the neonatal screening performed in your country?

Since 1.2.2009, **IRT1/IRT2/CI**

- positive CI in sweat test > 60 mmol/l, genetic examination - 65 mutations
- negative CI paediatrician follow up, in case of repeated respiratory tract infection or failure to thrive, control in CF centre
- increased attention, if the child was already ill, failure to thrive, or other circumstances (meconium ileus), or borderline CI in sweat, genetic examination
- positive screening – but negative sweat test - monitoring respiratory symptoms, weight, interview with parents (atypical CF ?) genetic examination. We are able to examine all genes for cystic fibrosis
- 2009 - 2014 : 329 738 newborns were examined (national screening centre Banská Bystrica)
- 43 CF were captured
- **incidence 1 : 7 668 live birth** (incidence before 1: 2 500)

4. Does actual National CF Registry exist in your country?
Yes, it is a part of ECFS PR since 2010

5. Do you have access to new therapies? Have you done some CF Clinical trials?
No, we dont have access to new therapy from Vertex in Slovakia. We have done a few clinical trials in Slovakia, but not new clinical trials with correctors and potentiators.

6.How you cooperate with national patients organisations? What do you expect from them ?
We have a very good cooperation with the patient organizations. Together we try to solve patients' problems. We are engaged in international cooperation. We expect from them:

- spread more information about the disease among caregivers, patients, and families, medical professionals
- help to support families and their children with CF
- offers support and social services to families and their children with CF, especially with a new patients with CF
- develop CF Centers, to improve the material and technical equipment in the centers
- lobbying for government support
- support clinical research, communiciation with CF patients about clinical research

7. What you feel are the main problems in CF care in your country?
Society, CF Centres:

- **financing**
- **health providers (beds, hygiene, separation)**
- **health insurance**
- **exception for therapy**
- **home i.v.**
- **home physiotherapy**
- **new expensive therapies**
- **lack of psychologists**
- **no administrative officer in CF centre**

CF Patients:

- **compliance**
- **therapy and physiotherapy**
- **psychological aspects**
- **accepting the diagnosis and treatment**

STANDARDS OF CARE FOR CF PATIENTS IN HUNGARY

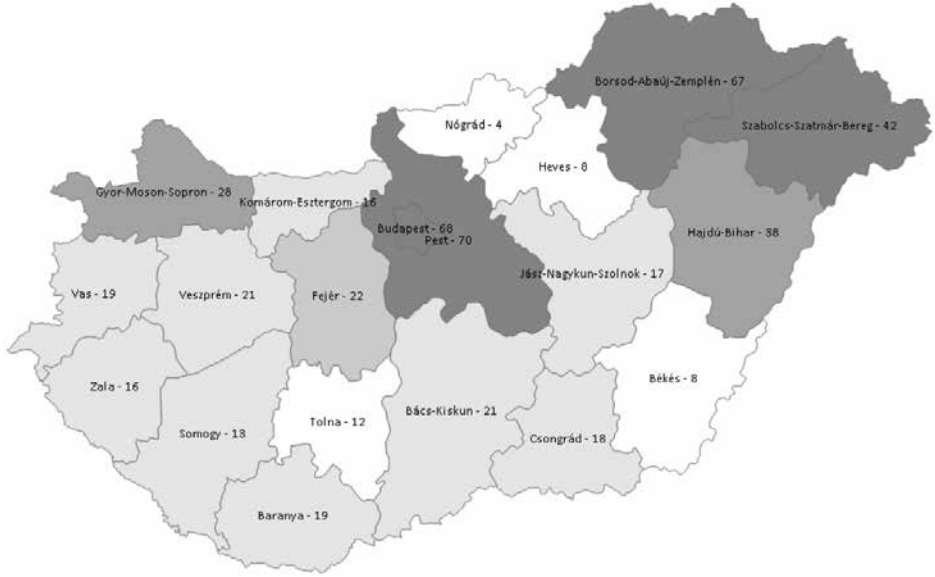
HALÁSZ Adrien, MD, PhD
National Koranyi Institute of Pulmonology, Department of Cystic Fibrosis, BUDAPEST

Country	**HUNGARY**
Population	**9 823 000**
Number of CF children	**278**
Number of CF Centers for children	**11**
Number of CF adults	**250**
Number of CF Centers for adults	**4**

Number of CFTR-related disorders patients: no exact data

1. How is CF care organized in your country: CF Center – CF team - Other specialists – what is their role in the system of care for CF patients in your country?

Number of patients by counties



The CF patients are treated in 11 children and 4 adult so called CF centers.
Unfortunately, only 3 of these centers meet the requirements of the European guidelines. There is one center servicing more than 100 patients and another two centers treat more

than 50 patients. The doctors working in the other 12 centers are also entitled to prescribe medication subsidized by the Hungarian Health System. The lack sufficient experience of the medical staff, doctors, physiotherapists, dietitians in CF treatment at the small centers means a considerable comparative disadvantage compared to the bigger centers.

2. Therapy: who pays the medicines and necessary equipment, transplantations, new therapies, how is the care paid, expensive therapies, orphan drugs? Insurance/patients? How physiotherapy is performed? At home, in the hospital, out-patient?
Above 90% of the prices of the medicines are covered by the Hungarian state thrue Health insurance. Pulmozyme, inhaled antibiotics, enzyme substitution is paid by the health insurance. Around 90% of the price of nebulizers are covered by the health insurance based on the personal request of the patients. The Chest Vests are available in the major centers, yet for patents it is not paid by the health insurance. Physiotherapy is taught to the patients at the centers and they are practiced it by themselves at home.
The availability of lung transplantation in Hungary is a main strength of the Hungarian CF care.

3. Is the neonatal screening performed in your country?
Neonatal screening is planned to be introduced soon - in 2019.

4. Does actual National CF Registry exist in your country?
Yes, since 2007. It is maintained by the Adult Organization of Patients with CF.

5. Do you have access to new therapies? Have you done some CF Clinical trials?
Inhalative antibiotics like Bramitob, Colomycin, Colobreathe are available and the price is fully covered by the health insurance in Hungary.
CFTR modifying therapy is not yet available.
Clinical studies had already been completed and some are still ongoing in several CF centers. No orphan drugs are paid.

6.How you cooperate with national patients organizations? What do you expect from them?
The major centers have close cooperation with patient's associations through jointly prepared financial support applications.
We expect patient's associations to improve deeper understanding by connecting the patients to work of the CF centers.

7. What you feel are the main problems in CF care in your country?

- **The number of dedicated centers that fulfils the EU guideline requirements is very limited - No specific CF Centers**
- **There is no audit of the activity of the CF centers**
- **How to involve young doctors?**
- **HOW to get the new medicines (Orkambi).**
- **The families have financial problems, so the mothers have to work, and they have no time and energy to make the treatments with their child.**

STANDARDS OF CARE FOR CF PATIENTS IN UKRAINE
Current Practice and Challenges. Data from Ukraine.

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Diagnostics of hereditary pathology department, 79008, Lysenko 31-A, LVIV UKRAINE
BOBER Lyudmyla, M.D., Chief of LVIV regional CF centre, 79035, Dnisterska, 27, LVIV UKRAINE

Country	**UKRAINE**
Population at 2017	**42 307 656**
Number of CF children	**620**
Number of CF Centers for children	**5**
Number of CF adults	**210**
Number of CF Centers for adults	**2** *(formal, just established)*

Number of CFTR-related disorders patients: about **50**
(CFTR-related disorders are rear diagnosed. Mostly CBAVD)

1.How is CF care organized in your country: CF Center – CF team - Other specialists – what is their role in the system of care for CF patients in your country?

Every 29-th – CFTR mutations heterozygous carrier
Expected frequency **1 - 3 364**
143 Cystic Fibrosis children are expected to be born every year in Ukraine
1700 - 4000 CF patients are expected to be exist in Ukraine

Ukraine – post Soviet Union country where CF care is not as good as than generally in Europe and many CF patients died to early.

No official recognition of term “CF centre”

CF Diagnostic:
- Many CF patients are undiagnosed
- Sweat testing by pilocarpine iontophoresis is still a challenge; number and performance need improvement .
- Macroduct, Nanoduct are available only in few sites.
- New Guidelines for CF treatment adopted by Ministry of Health in 2016.
- The big improvement with medication access. National program. Not all antibiotics are accessed *(Generics!)*
- No one CF adult specialist
- Not all sited has specialist on physiotherapy, psychologist, No CF dietician.

24 Oblasts Children's Hospital (pulmonology, pediatrician, gastroenterology departments)
3 CF centers for children (>50 patients)
2 mixed centers

2.Therapy: who pays the medicines and necessary equipments, transplantations, new therapies,....? How is the care paid, expensive therapie, orphan drugs? Insurance/patients ? How physiotherapy is performed? At home, in the hospital, out-patient ?
There is National program to supply CF patient with enzymes, dornase alfa. There are few regional program to supply CF patient from some territory. Patients should commonly pay for flutters, nebulizers, vitamins, etc. Physiotherapy is performed in the hospital as usual.

3. Is the neonatal screening performed in your country?
IRT/IRT CF-NBS screening program

- The CF NBS by two steps IRT/IRT was started in the whole country in 2012 and was discontinued in 2015 – 2016.
- The CF NBS protocol was integrated into the current blood spot screening program.
- The cut-off for IRT-1 was set at 70 ng/ml, IRT-2 - 40 ng/ml.
- Next step was sweat testing followed by DNA test in case of sweat Cl level was over 30 mmol/l.
- In 2018 restarting of IRT CF-NBS screening program is planned.

The educational activities should be done to improve the benefits and justify the financial costs of restarting of CF-NBS program.

4. Does actual National CF Registry exist in your country?
No national CF registry.

Since 2011 data are included in ECFSPR
- only 1 center;
- motivation of Ministry and other clinics to joint registry,
- collecting on National data

Comparing:
- Lover BMI,
- Higher incidence of *Pseudomonas aeroginosa infection*
- The oldest CF patient is 34;
- No one CF patient from UA was transplanted

5. Do you have access to new therapies? Have you done some CF Clinical trials?
No access to new therapies.
No one CF Clinical trial on new therapies was performed in Ukraine.

6. How you cooperate with national patients organizations? What do you expect from them ?
- The collaboration with regional office mostly. The main joint activities: support of newly diagnosed patient's families, lobby for funds for CF care, information campaign, support of poor families.
- Expectation: support of ECFS PR instituting in Ukraine; true collaboration with national patient's organisations, the using of the best practice for establishing CF care, education program

7. What you feel are the main problems in CF care in your country?
- **Lack of the knowlege about CF among specialist and parents of CF patients.**
- **The old „post Soviet union"system of Medical care in Ukraine.**
- **Lack of financial resources.**
- **No access to new therapies.**
- **No access to transplantations.**

STANDARDS OF CARE FOR CF PATIENTS IN BELARUS

BARADZINA Halina, MANAVITSKAYA Natalia, VOITKO Tatyana
Belarussian State Medical University, MINSK, BELARUS

Country	**THE REPUBLIC OF BELARUS**
Population	**9 498 000**
Number of CF children	**150**
Number of CF Centers for children	**1**
Number of CF adults	**52**
Number of CF Centers for adults	**2**
Number of CFTR-related disorders patients	??

1.How is CF care organized in your country: CF Center – CF team - Other specialists – what is their role in the system of care for CF patients in your country?

We have no CF centers according to the European consensus. These are “treatment facilities” approved by Ministry of Health. There are no special outpatient clinics. Our outpatient clinic is an institution where special hours for CF patients are reserved. All the doctors who work in the Centers, have experience in CF.

THE CENTERS HAVE NO SPECIAL FINANCIAL SUPPORT

1 CF Center for children is a part of children hospital N3 in Minsk
2 CF Centers for adults are part of big clinical hospitals:
1 – for Minsk citizens
1 – for people from other places

CF patients from different places can get consultation and treatment on a regular basis in the Regional Hospital (pulmonology department). There are educated specialists:
pediatrician
pulmonologist
physiotherapist.

CF team. Who is a member of the CF team?
There are no real CF teams and special staff for CF in Belarus.
All specialists are available in these Hospital similarly to other patients.
CF patients are managed by a doctor – a pulmonologist or a children's pulmonologist. Doctors, who treat CF, also work with other pulmonary diseases. CF patients are a small proportion of their patients (about 5 - 10%).
Physiotherapists work with CF patients systematically. There is no regular basis consultations by nutritionist in our centers. There is a very limited number of those specialists in Belarus.
Psychological support isn't provided to CF patients and their families regularly.

Protocols of CF adults rehabilitation were composed in the Center and approved by the Ministry of Health in 2009.The pilot project for the rehabilitation of adult patients with CF was funded by the Government.
A CF team consisting of:
pulmonologist,
physiotherapist,
specialist for nutritional support,
psychologist was created during this period.
As a result of this project we have an official Protocol of CF adult patients rehabilitation from 2009.

Services for CF patients **(In-patient):**
Indications for CF patients hospitalization:
- regular courses of ATB therapy - every 4 months on average
- acute situations, that require hospitalization
- CF complications
Unfortunately adult patients stay in the same space with other patients in CF Centers

Services for CF patients **(out-patient):**
- CF patient check-ups every 3 months on average (every month if necessary)
- In acute situations – at GP or local pediatrician, CF patients come to CF Centers in hospital as a rule

The type of mutations was identified in 83% of CF patients in Belarus now. The most common mutation - DF508 (62.2 % of CF patients).

Currently 30 most common mutations of the CFTR gene have been identified in Belarus. We hope that identification of 70 mutations of the CFTR gene will be available by means of genomic sequencing starting from 2018.
With a high risk of developing CF in a child (both parents have mutation carriers), **preimplantation diagnosis is possible.**
CF patients receive treatment according to the **National Clinical protocol of diagnosis, treatment and rehabilitation of patients with cystic fibrosis** which is sufficient following the European consensus (Order of the Ministry of Health No. 1536 of 2012).

2.Therapy: who pays the medicines and necessary equipments, transplantations, new therapies,....? How is the care paid, expensive therapie, orphan drugs? Insurance/patients ? How physiotherapy is performed? At home, in the hospital, out-patient ?
Health care service (including transplantation) in all the state medical institutions (in-patient and out-patient) is **free for all people in Belarus** (not only CF patients) and is completely covered by the Government.

Children with CF receive all medicines free of charge (not only essential CF drugs, but also medicines for other diseases).
The cost of one CF child treatment course is 10 - 25 thousand dollars per year in Belarus.
There is no developed insurance medicine and reimbursement system in Belarus.
All adult patients with CF receive the pancreatic enzymes (Creon) free.
Adult CF patients, who have a disability, buy medicines, manufactured in Belarus, with a discount, depending on the degree of disability (high degree - 90% discount, mild - 50% discount). The difference is covered by the Government.

Currently most medicines that are used in the world for CF treatment are available in our country, because many of them have been manufactured in Belarus (generics).
Many patients with CF receive therapy including ursodeoxycholic acid daily

Inhalation:

- hypertonic (7%) sodium chloride solution
- mannitol
- dornasa alfa
- beta-agonists of short and long action
- selective cholinoblockers
- combined drugs

Antibacterial drugs of all groups are freely available for the CF patients in Belarus:

- penicillins
- III and IV generations of cephalosporins, carbapenems
- aminoglycosides
- glycopeptides
- quinolones
- aminoglycosids for inhalation
- sodium colistimethate for inhalation
- macrolides are included in standard protocols for long-term use in subinhibitory doses in patients with CF.

Physiotherapy - the following methods are used:

- postural drainage
- manual percussion of the thorax
- autogenous drainage
- active breathing cycle
- positive expiratory pressure with the help of PEP-systems
- chest massage
- sports training

All patients and their parents have been educated in the methods of kinesitherapy and respiratory physiotherapy.
Physiotherapists have been trained in Italy.

All patients are provided with PEP-masks and nebulizers (with the help of the Italian Foundation "Help them to live'')

Big progress has been made in transplantation development in Belarus during the last 3 years. We have had some successful lung transplantations (and 1 – lung and heart complex) in different lung diseases.
The first lung transplantation has been successfully attempted in CF patients in Belarus in December 2017. One more patient with CF has been already included in the "waiting list" for the lung transplantation.

3. Is the neonatal screening performed in your country?
Neonatal screening for CF was performed only in 1995 - 1996 in Belarus. It was found that the incidence of CF in Belarus is **1 : 8 150 newborns.**
Totally 146 701 newborns were screened and 1 085 (0.74%) of them had IRT value above the norm. In the first 337 positive samples direct analysis on 5 CFTR gene mutations (dF508, G542X, N1303K, V1282X, R553X) reviled 18 newborns with dF508 *(N. Mosse, K. Mosse).*
It was the only pilot study. **Now we have no neonatal screening**.
The detection of CF is more than 6 times lower than in 1995 - 1996.
It is planned that neonatal screening for CF will be available for all newborns in Belarus in the nearest future.

4. Does actual National CF Registry exist in your country?
There is no National CF Registry in Belarus at the moment.
Specialists work on the creation of a register and it is hoped that it will be created next year.

5. Do you have access to new therapies? Have you done some CF Clinical trials?
Gene therapy methods are not used in Belarus now.
Correctors of mutant CFTR protein have not been registered yet.
Clinical trials of new drugs in patients with CF have not been performed in Belarus.
Belarus was invited to participate in gene therapy trial by Russia, but there were no patients corresponding to the criteria for inclusion.

6.How you cooperate with national patients organisations? What do you expect from them ?

Association of CF patients – parents was created in 1994. Chairwoman is N.S. Dobrova

"Association for the Salvation of Children"

All of our CF centers have been opened thanks to financial support of the **Italian Foundation "Help them to live"** and the Italian charitable association "Alba". These organizations regularly supplied our Centers with vital medicines, as well as nebulizers, PEP - masks and other equipment. Training courses for the pediatricians, physiotherapists, pulmonologists and nurses were organized at the Center of CF in Verona in 1996 - 2004.

7. What you feel are the main problems in CF care in your country ?

- **The medical environment is trying to implement the European standards in Belarus.**
- **There is no national registry of patients with CF**
- **There is no neonatal screening for CF**
- **The absence of real CF centers and a CF teams with educated nutritionists and psychologists**
- **The absence of new medicines (correctors and potenciators of mutant CFTR protein)**

NEW THERAPIES - PIPELINE

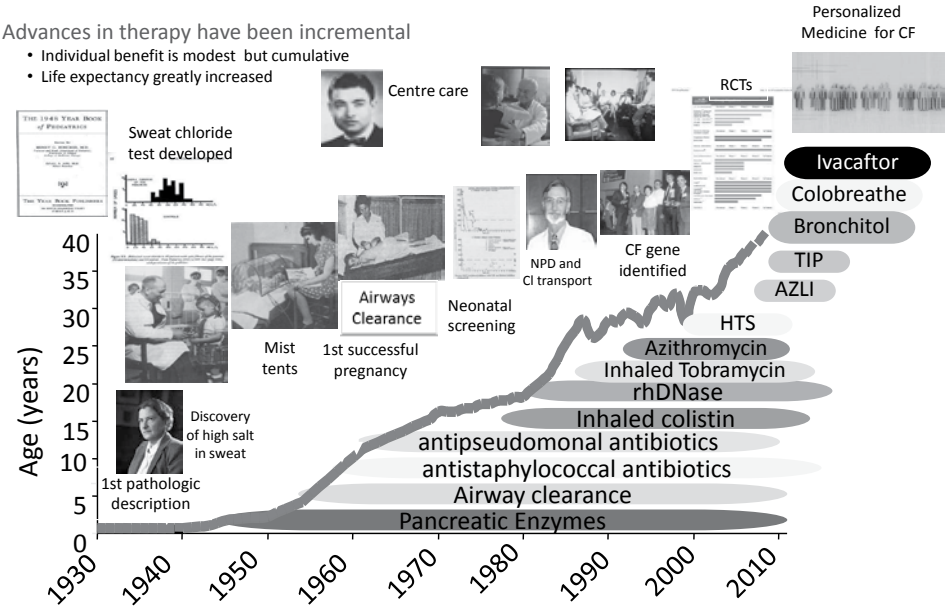
SANDS Dorota Prof. – President of Polish CF Society, Institute of Mother and Child in Warsaw
Head of CF Center DZIEKANOW LEŚNY, POLAND

Personalized CF Regimens

- Maximize CFTR function
- Initially based on the patient's CFTR mutations
- Ultimately a personalized response may be used
- Symptomatic therapies will be utilized as needed
- Infants and young children with excellent CFTR restoration may not need other therapies
- Understanding impact of various levels of CFTR restoration will help us determine what additional therapies are needed to maintain health
- Older patients with established **disease will probably continue to need other therapies**

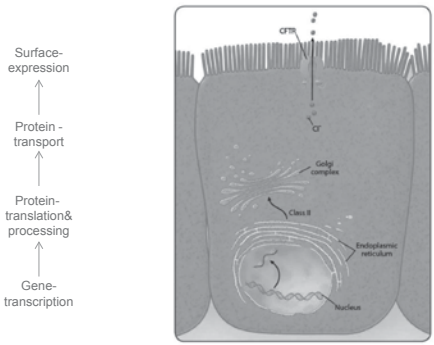
Improved Survival with Treatment Innovation

Incremental/ Modest Benefits



CFTR: gene and protein

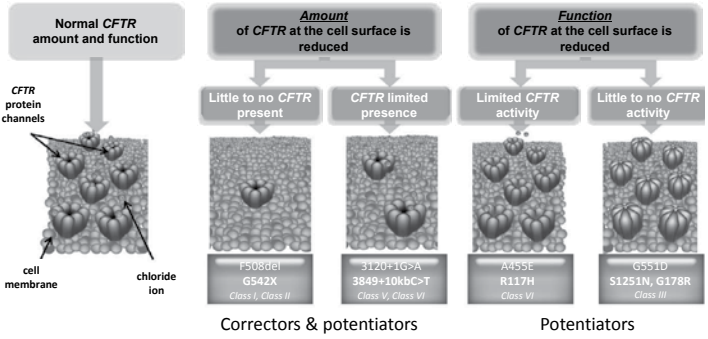
- Normal production of *CFTR* protein consists of different processes[1]



Afbeelding is een aangepaste versie van Rowe et al. 2005.2
1. MacDonald KD et al. Pediatr Drugs. 2007;9:1-10. 2. Rowe SM et al. N Engl J Med. 2005;352:1992-2001.

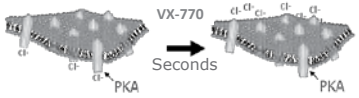
CFTR gene mutations reduce the amount and/or function of the *CFTR* protein channel

- Different gene mutations (~1900) result in *CFTR* channel dysfunction[1-3]

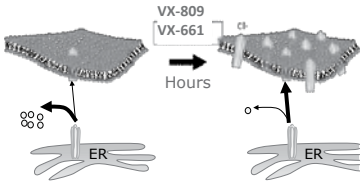


Two approaches to increase CFTR function

Potentiators:
Increase the flow of ions through activated CFTR present at the cell surface

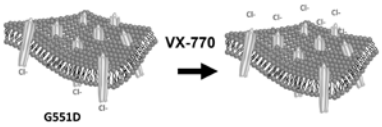


Correctors:
Increase the cellular processing and delivery of CFTR proteins, such as F508del-CFTR, to the cell surface

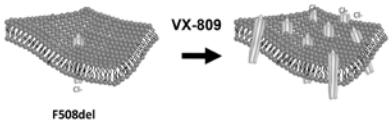


- Orally bioavailable drugs
- Two CFTR targets:

Potentiators:
Increase opening (gating) of CFTR channels

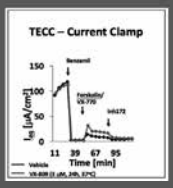


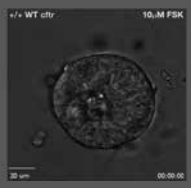
Correctors:
Increase number and function of CFTR channels at the cell surface



Theratyping:

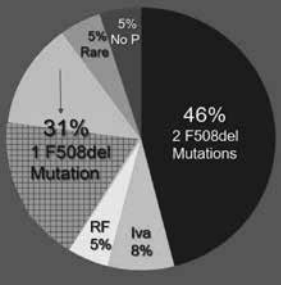
Laboratory testing of *CFTR* mutations using cell lines to determine which available modulators they respond to





2017: A Breakthrough Year for Modulators

1) Better therapies for those already on modulators
2) Residual function mutations treatment
3) Ability to assess rare mutations
4) Single F508del mutation treatment
5) Class I mutations treatment



Ivacaftor Label: May 17, 2017

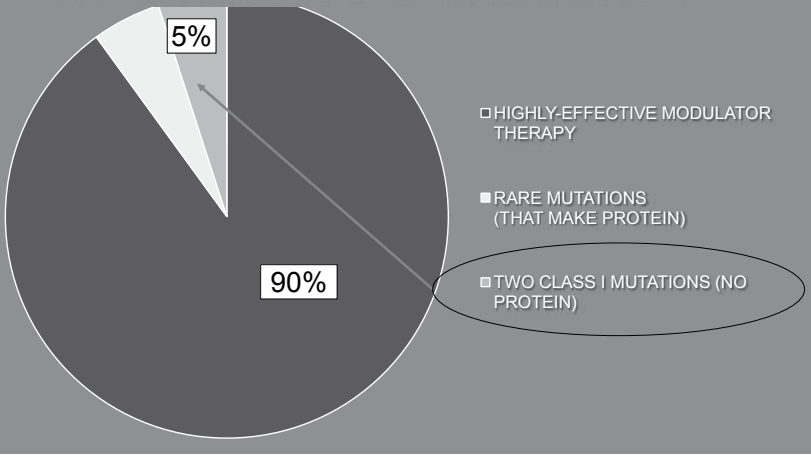
----------INDICATIONS AND USAGE----------

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one mutation in the *CFTR* gene that is responsive to ivacaftor based on clinical and/or in vitro assay data. (12.1, 14)

FDA Opens the Door to Use of In-Vitro Testing to Assess Rare Mutations Modulator Response

The U.S. Food and Drug Administration today expanded the approved use of Kalydeco (ivacaftor) for treating cystic fibrosis. The approval triples the number of rare gene mutations that the drug can now treat, expanding the indication from the treatment of 10 mutations, to 33. The agency based its decision, in part, on the results of laboratory testing, which it used in conjunction with evidence from earlier human clinical trials. The approach provides a pathway for adding additional, rare

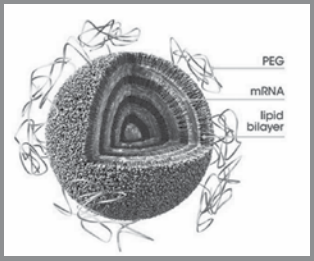
The Last 5%: Two Class I Mutations



Coming Soon: CFTR RNA Delivery and Repair

RNA delivery

- Translate bio
- Delivery of CFTR mRNA
- Clinical trial 2018



RNA repair

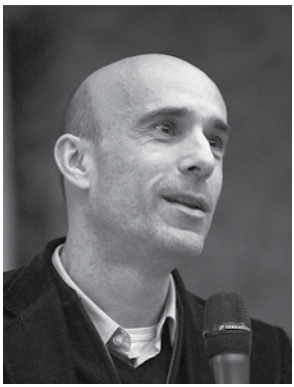
- ProQR
- QR-010 – demonstrated POC in two F508del mutations
- Mutation-specific repair of common stop mutations

Summary

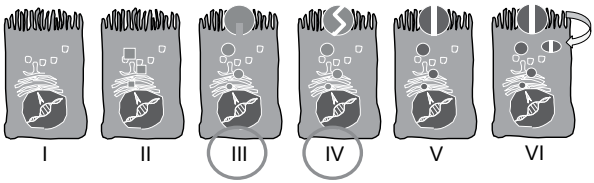
- **CF is a genetic disorder that results in absent or non-functional CFTR protein affecting many organ systems**
  - **Results in thick, viscous mucus**
- **Pharmacokinetics differ in the CF population**
  - **Higher volume of distribution**
  - **Faster metabolism and elimination**
- **Previous drug treatments targeted symptoms and infectious organisms**
- **New and investigational treatments are focused on making the CFTR protein function properly**

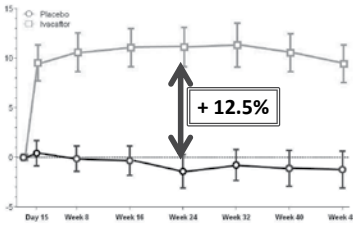
NEW THERAPIES - PIPELINE

DREVINEK Pavel
Department of Medical Microbiology & Prague CF Centre
2nd Faculty of Medicine, Charles University, Motol University Hospital, PRAGUE, CZ

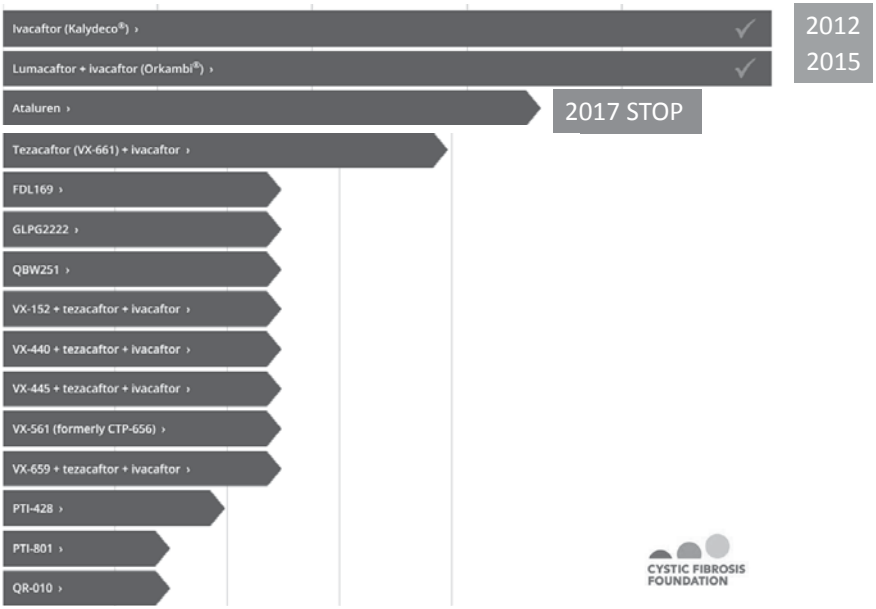


Ivacaftor (Kalydeco) = CFTR potentiator





CFTR Modulators: potentiators, correctors, amplifiers

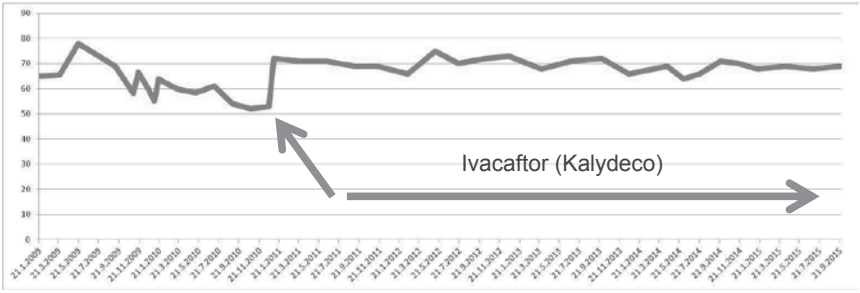


Jakub, 28 years old

CF: sweat test 86 mmol/L; F508del/G551D

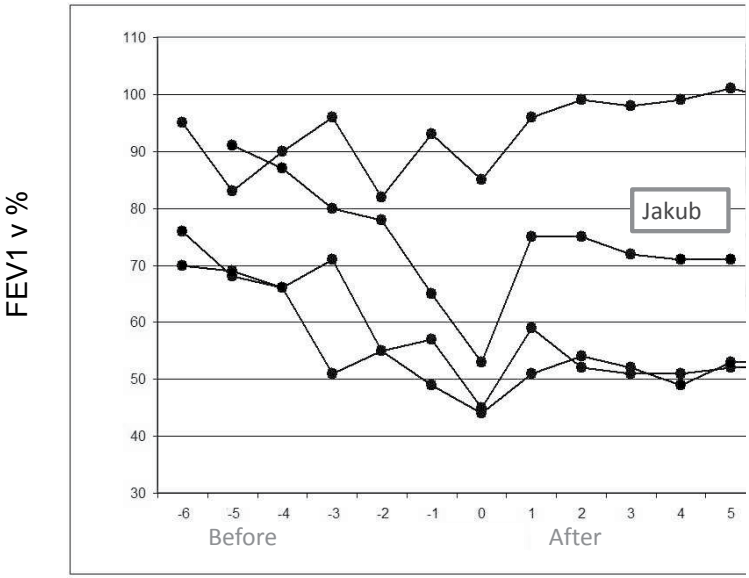
- pancreatic insufficiency
- CF related diabetes
- liver disease
- chronic infection with *S. aureus, P. aeruginosa*

FEV1 %



19.5 yrs 20.5 yrs 21.5 yrs 22.5 yrs 23.5 yrs 24.5 yrs 25.5 yrs

Ivacaftor in the Czech Republic:



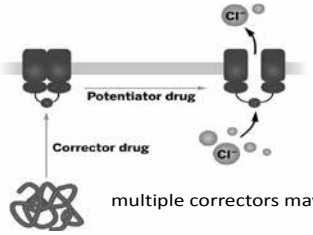
VX-440

1st generation corrector

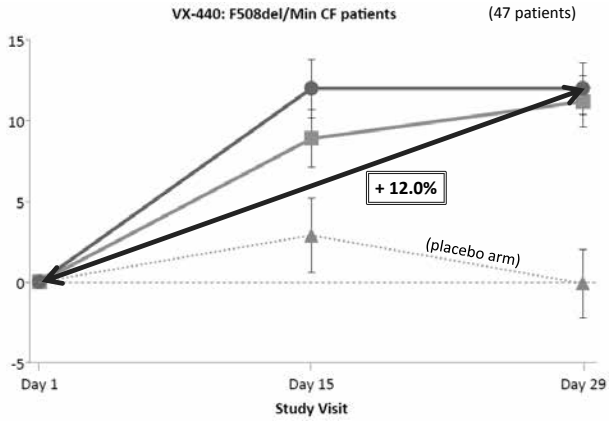
potentiator

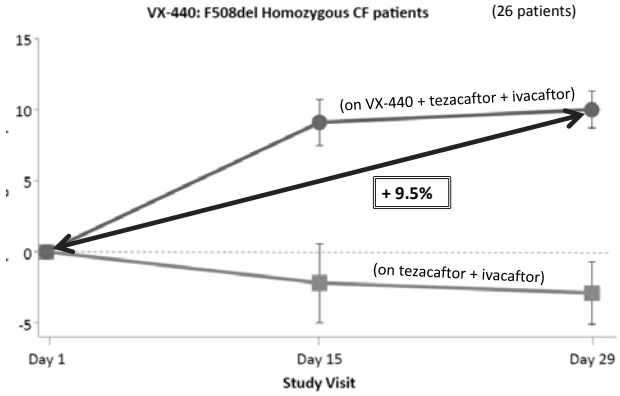
VERTEX

mechanism of action	**second generation CFTR corrector**
In combination with	tezacaftor and ivacaftor
route of administration	oral
target population	**F508 del/minimal function, F508 del/F508 del**
Phase	2



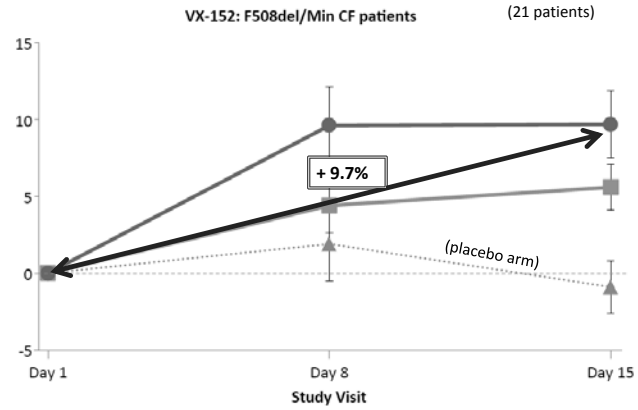
multiple correctors may be required for optimal folding

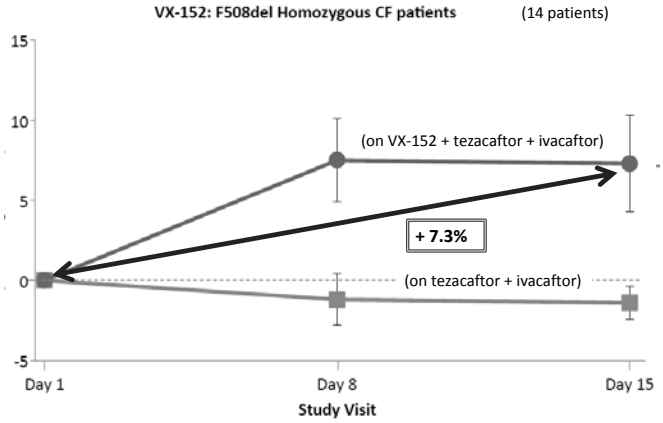




VX-152

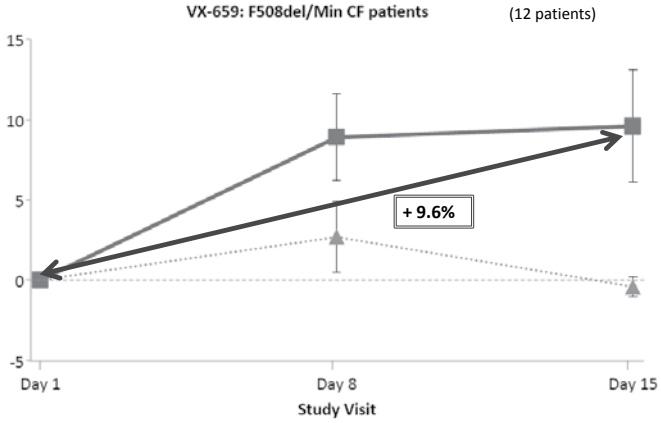
mechanism of action	**second generation CFTR corrector**
In combination with	tezacaftor and ivacaftor
route of administration	oral
target population	**F508 del/minimal function,** **F508 del/F508 del**
Phase	2



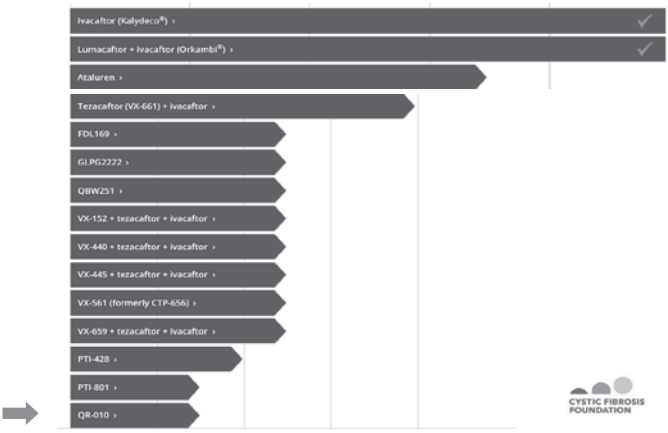


VX-659 **VX-445**

mechanism of action	**second generation CFTR corrector**
In combination with	tezacaftor and ivacaftor
route of administration	oral
target population	**F508 del/minimal function, F508 del/F508 del**
Phase	1



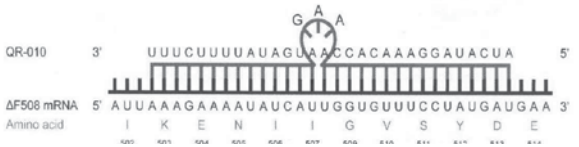
CFTR Modulators: potentiators, correctors, amplifiers



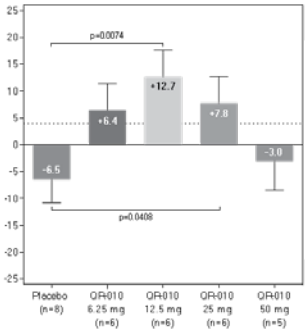
N.B.Post conference note: In February 2018, Vertex announced selection of two next - generation correctors, **VX-659** and **VX-445**, for further testing (in phase III clinical trials)

QR-010

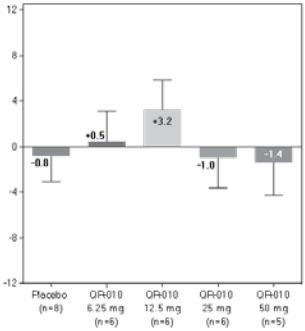
mechanism of action	**editing of mutated RNA**
In combination with	-
route of administration	inhalation
target population	**F508 del/F508 del**
Phase	1



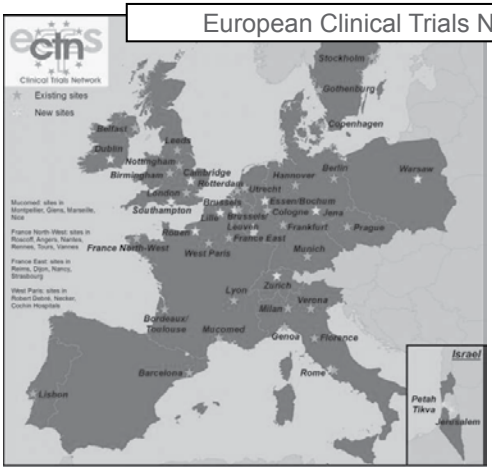
Questionnaire on respiratory symptoms



FEV1



European Clinical Trials Network



43 CF centres from 15 countries

THE EUROPEAN CYSTIC FIBROSIS SOCIETY PATIENT REGISTRY (ECFS PR)

NAEHRLICH Lutz, ECFS, GERMANY

Why is a European CF Registry necessary?
To get a good picture of cystic fibrosis it is important to collect data from as many patients as possible.

- **Compare the centres and countries**
- **Outcomes of the comparisons give insight in the disease**
- **Data for research**

31 countries > 42,000 patients
Longitudinal data: 2008 - 2015

Mission:
Compare aspects of CF and its treatment to...

- Encourage new standards of CF care
- Inform public health planning
- Enable research

Value of the Registry

Patients & their families	Information about outcomes in the country to discuss with doctor Enhance CF-care, access to new therapies
Patient Organisations CF Europe	Lobby for CF-care with heathcare authorities and other parties
CF centres	Compare with other centres and countries Monitor quality of care & identify areas for improvement
Researchers	Longitudinal and large-scale epidemiological research Identify disease modifying factors
Healthcare authorities	Information about CF and CF-care
Industry	Prepare the landscape for clinical trials Monitor effectivess & safety of new therapies

Data Collection

Anonymized Data
Consented Patients

SOFTWARE

Variables

Demographic	age, gender, status of patient
Diagnosis	age at diagnosis, sweat test, meconium Ileus, neonatal screening
Genotype	1st and 2nd mutation
Growth / lung function	value of best FEV1 and FVC, height and weight at best FEV1
Microbiology	Pseudomonas aeruginosa, Staphylococcus aureus, Burkholderia cepacia
Complications	Diabetes, liver disease, pancreatic status, malignancy
Therapy	antibiotic, bronchodilators, oxygen therapy, pancreatic enzymes
Transplant	Lung / liver transplant

General Features

ECFSTracker
European Cystic Fibrosis Society Patient Registry

A platform for the collection of CF data for all purposes

- ✓ Web-based and open source
- ✓ Designed for the collection of CF data
- ✓ User friendly
- ✓ Remotely managed
- ✓ Data quality checks on different levels

Data Protection - Security

- ✓ Advanced Security Technology
- ✓ Controlled user access
- ✓ De-identification of data:
  encryption of data during transmission
- ✓ Compliant with EU data protection regulations

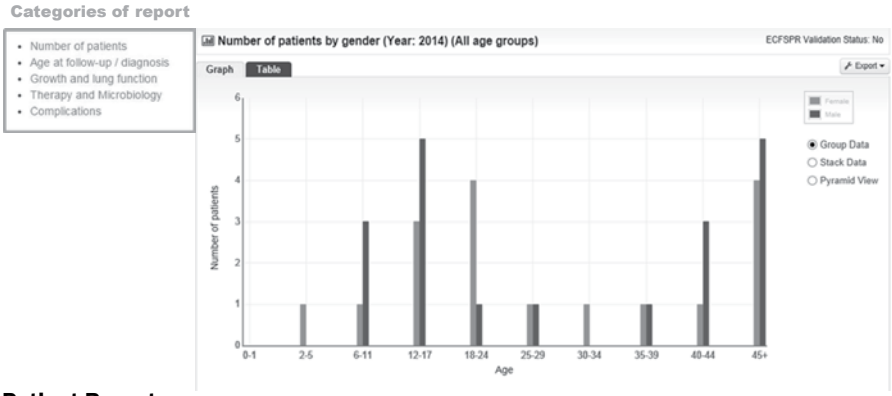
ECFSTracker - dashboard

ECFSTracker - homepage

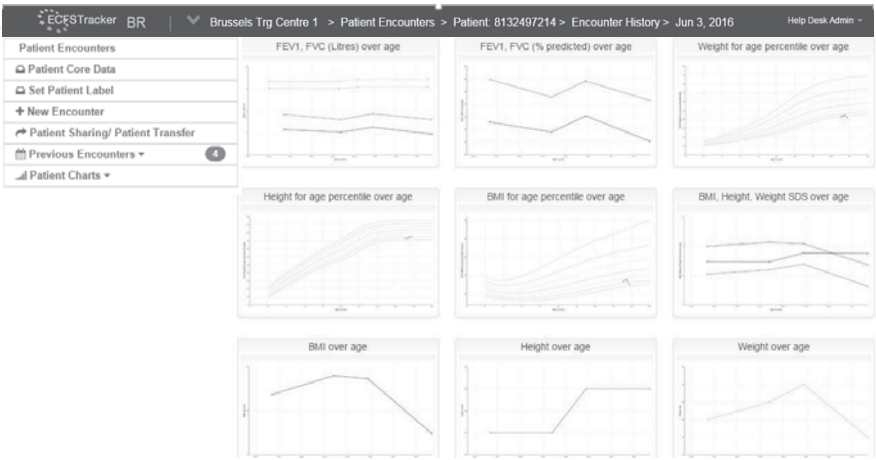
Annual summary

Encounters

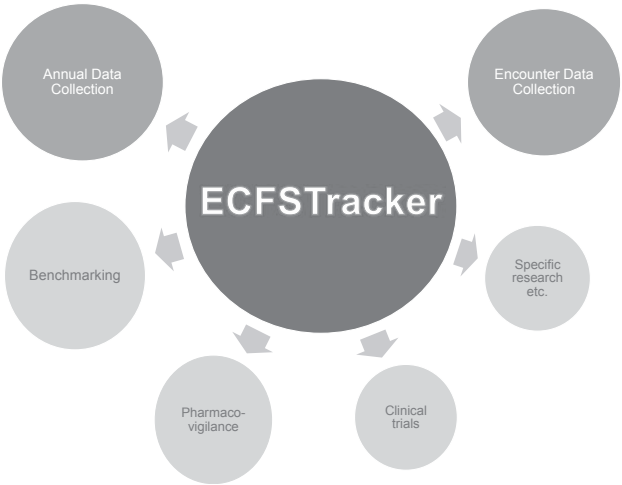
Centre Reports



Patient Reports



Development



Upgrade to version 2.0

TImelines:

Development: 2017 - 2018
Test in pilot countries
Launch in Europe: 2019

Benchmarking

A module in ECFSTracker to allow cross-comparison of indicators of quality of care (= benchmarks).

↓

Direct feedback to Centre Staff

↓

Identify areas for improvement

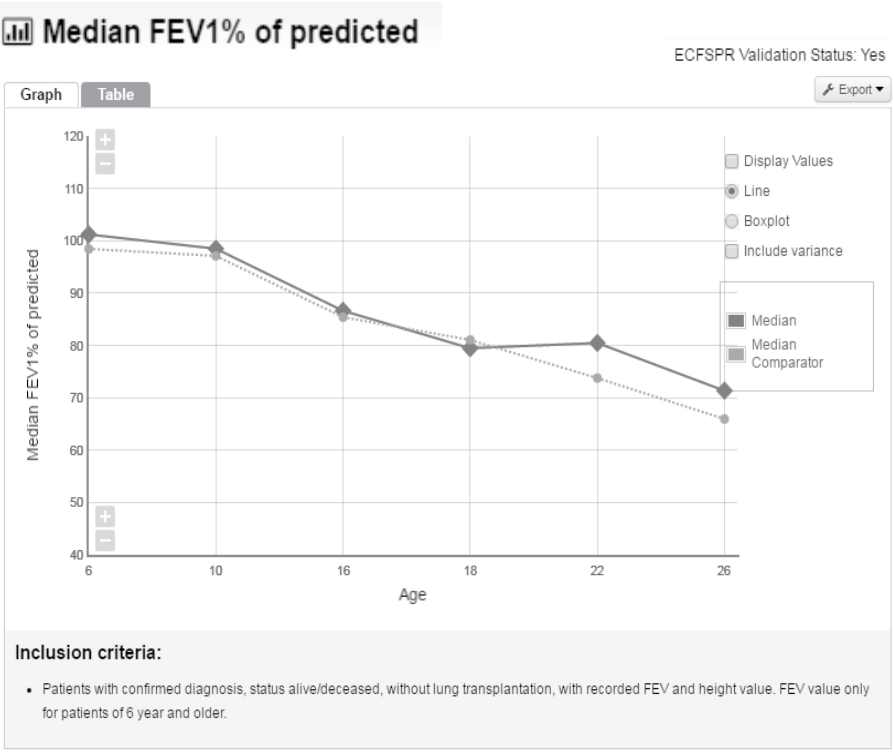
A powerful tool to enhance improvement of CF care

Compare results between:

Your country with another country / other countries
Your centre with another country / other countries
Your centre with other centres in your country

Agreement between centres!

Compare with previous years



PROJECTS : Overview

1. Definitions Group

Review variables and definitions

2. Global CF harmonisationproject

Harmonisevariables & definitions to allow comparison ww

3. Patient awareness project

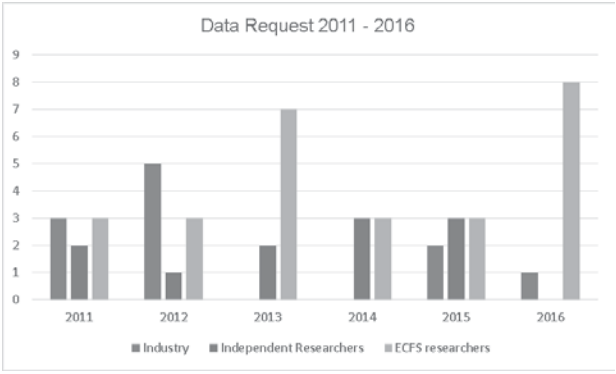
Joint effort with CF Europe to bring data closer to patients

4. Data Quality Group

Ensure accuracy and quality of data

OUTPUT

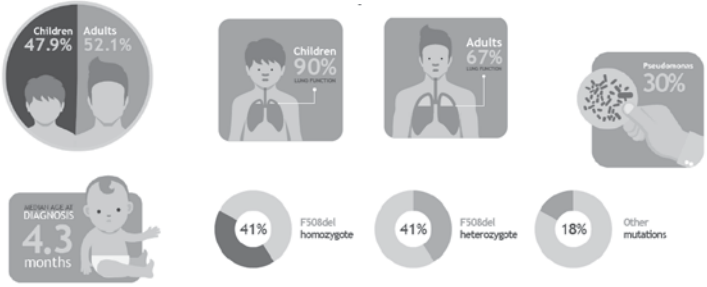
Research



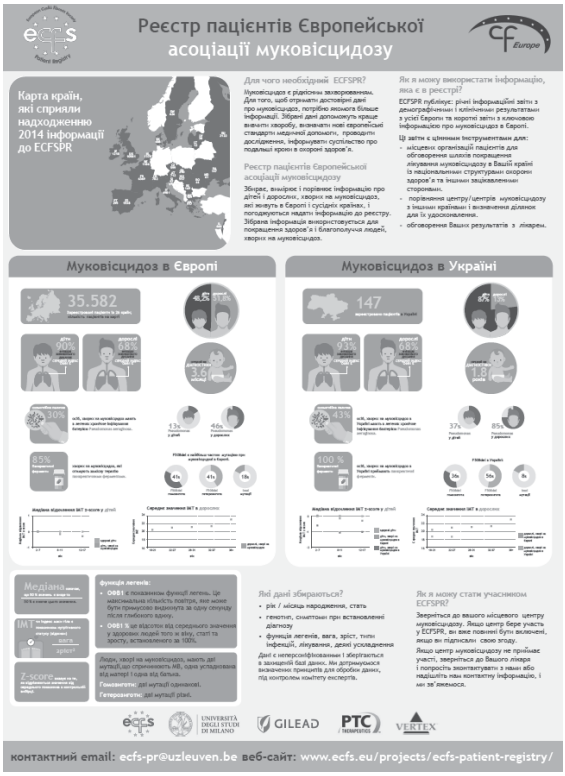
Manuscripts in the pipeline

- International and pan-European comparison of survival in CF.
- Changes in demography and clinical outcomes in CF in Europe.
- Mortality during pediatric age in patients with CF in Europe.
- The effect of CFTR nonsense mutations on phenotype and mortality in patients with CF.
- The effect of DNase on longitudinal lung function in patients with CF.
- Clinical characteristics of CFRD: Lessons from the ECFSPR.
- The effect of Allergic Bronchopulmonary Aspergillosis on lung function in children and adolescents with CF: analysis of the ECFSPR data.
- CF-specific reference equations for FEV1 and BMI: an updated analysis.
- Cancer in adult people with CF in Europe.

At-a-Glance Reports



Poster



How to set-up national registry?

How to join the ECFSPR?

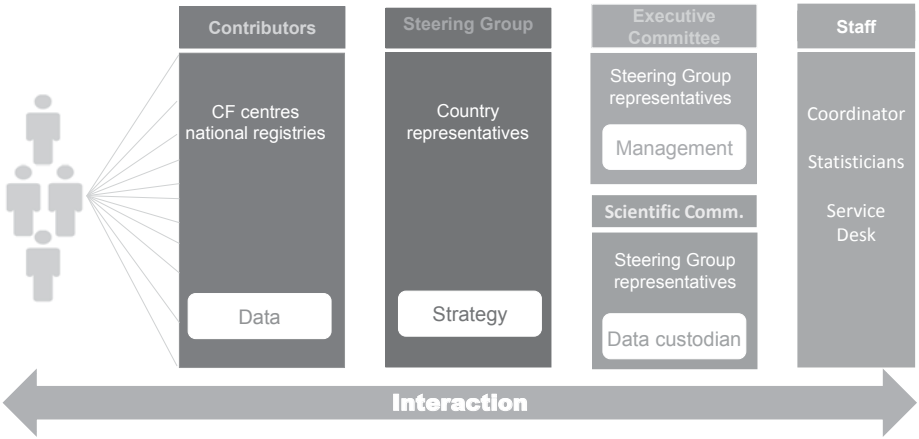
- ➢ Legal and Ethical approval
- ➢ Informed Patients Consents
  - ECFSPR templates on website
  - Meet requirements of your local legal and ethics laws
  - Translate to your own language

GOVERNANCE

Documents:

1. **Terms of Reference:** Registry's structure
2. **Code of Conduct:** roles and responsibilities
3. **Standard Operating Procedures:**
   - Data Collection & Error reporting
   - Data Access
   - Use of data
4. **Business Plan** 2015 - 2018

Organisation



What to expect from ECFS PR?

1. **Software & Training & Support**
2. **Opportunities to be engaged in research projects**
3. **Information & documents**
4. **Network to share experience & exchange ideas**
5. **Support to promote the value of a (European) registry at national CF meetings**

http://www.ecfs.eu/ecfspr
mailto:ecfs-pr@uzleuven.be

The European Registry is a useful tool to help to understand CF and benefit people with CF

POLISH CF REGISTRY?

SANDS Dorota Prof. – President of Polish CF Society, Institute of Mother and Child in Warsaw
Head of CF Center DZIEKANOW LEŚNY, POLAND

No Registry

Historic registry

Registry needed !

Polish CF Patients' Registry

estimated 2000 patients
(according to PCFS)

- 1661 registered patients
- 1552 living patients

1017 children	**(0-18 years)**	**65,5%**
535 adults	(>18 years)	34,5%

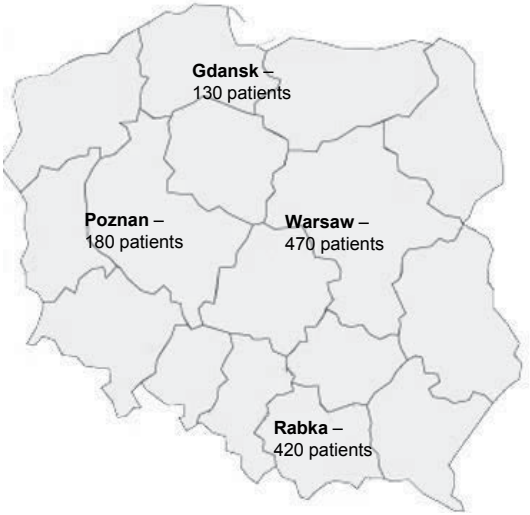
Source: A. Pogorzelski, Conference PCFS 2012

Polish CF Patients' Registry

estimated 2900 patients
(according to NHS data)

2002 children	**(0-18 years)**	**68,59%**
917 adults	(>18 years)	31,41%

Cystic fibrosis centers



4 LEADING CENTERS

Missing…

- Data protection agency paper

Ready (almost) to join European Registry

CF PATIENTS REGISTRY IN HUNGARY

MARSAL Géza, vice president
Hungarian Association of Cystic Fibrosis Adults, HUNGARY

The Hungarian CF Patient´s Registry is provided since 2007 by organization **Hungarian Association of Cystic Fibrosis Adults.**

Total number of CF persons in Hungary in 2015 **567**

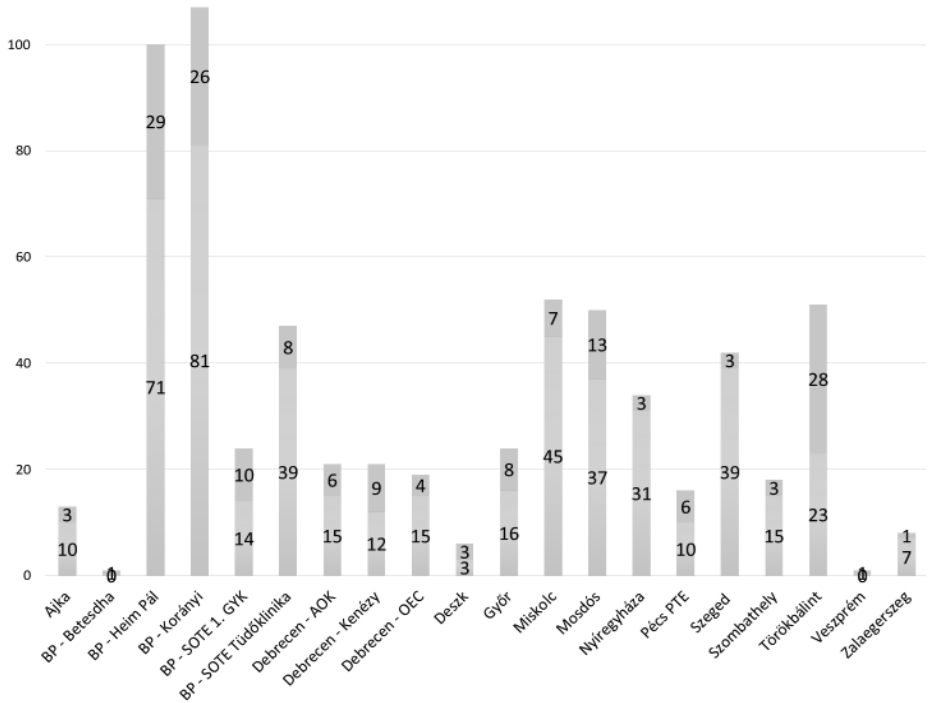
Hungarians CF frequency **1 : 4 000**

There are 18 different locations in Hungary where CF care is currently available.

The biggest centers are Heim Pál Hospital (children) and Korányi Institute (adult). Both are located in Budapest.

In some cases patients are registered at two or more centers in the same time. The reason of this is mostly the running transition from the pediatric care to the adult center or the distance of the centers.

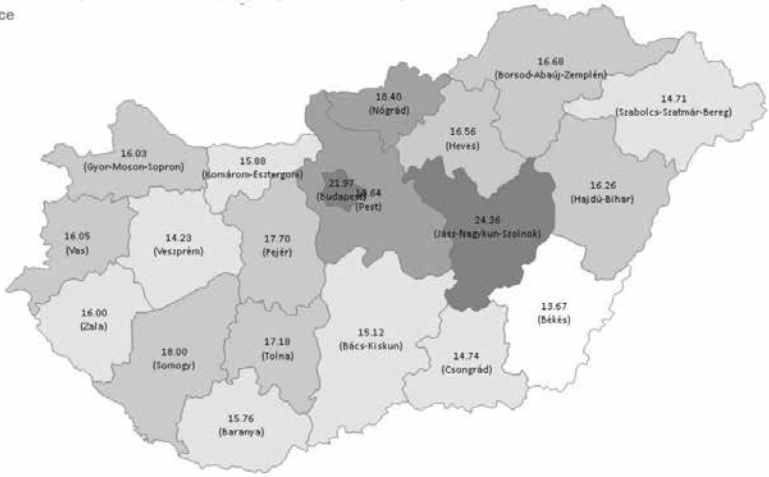
NUMBER OF PATIENTS BY CENTERS



AVERAGE AGE BY COUNTIES

Average age by residence

9

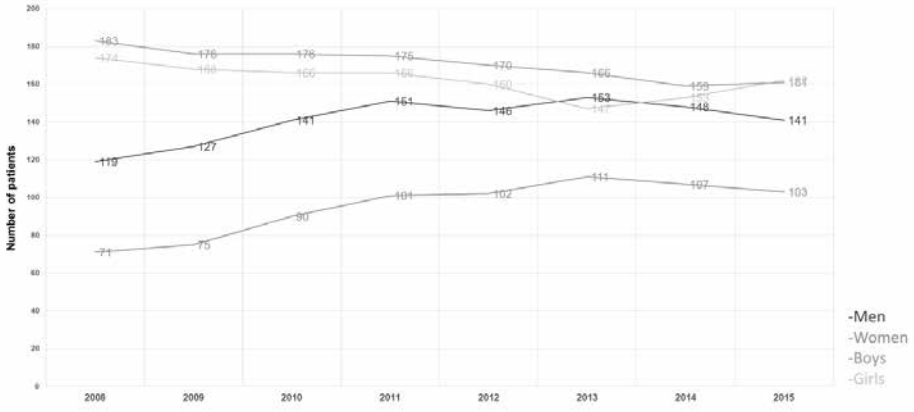


Most / least populated counties in Hungary:

- Pest: 69
- Jász-Nagykun-Szolnok: 19
- Nógrád: 5

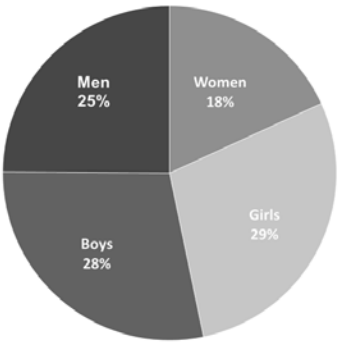
NUMBER OF PATIENTS BY GENDER

6



DISTRIBUTION BY GENDER

5



TOTAL NUMBER OF PATIENTS: 567

Men: 302

Women: 265

AVERAGE AGE

Men: 17,8 years

Women: 16,4 years

CYSTIC FIBROSIS - WHEN WE COULD NAME IT AND RECOGNIZE IN THE LESSER POLAND VOIVODESHIP

KURTYKA Zuzanna
Woj. Spec. Szpital Dziecięcy, im. św. Ludwika, Oddział Pulmonologii, KRAKOW, POLAND

WORLD HISTORY of CF

1905 - first anatomical description
1936 - **Fanconi** for the first time described **symptoms typical for CF**
1938 - **Doroty Anderson** called new illness **Cystic Fibrosis of the Pancreas**
1944 - **Faber** introduced new name: **mucoviscidosis**

Earlier there were only anatomical descriptions of individual symptoms:
1595 Leiden
1673 Toruń
1677 Amsterdam

Child - fight for human rights
By XVI c. a child was treated as a thing, easy to be manipulated and controled
In the end of XVII c. – beginnig of XX c. philosophy of enlightenment brought personality and subjectivity to a child: *JJ Rouseau, Jonh Lock, Janusz Korczak*
In **1900** *Elen Key* wrote a book named „Child Century" and called for the child's independence and personal freedom. She hoped that XX c. would be the century of happiness for children .
Unfortunatelly **XX c**. brought fear, death, and pain to them.

When did a child become a patient for doctors?
In the second half of XIX c, in Kraków in **1872 Society of Medical Care for Children** was created by Princess Marcelina Czartoryska and the doctor Leon Jakubowski. At that time children mortality in Kraków was 50 % and 80% in neightboring Galicja region.
In **1876 St. Ludwik Children Hospital** at Krzyżowa str. came into existance.


SZPITAL
Śgo LUDWIKA
W KRAKOWIE
(na łóżek 72).
Opisał
Profesor Dr. Maciéj Leon Jakubowski.
W Krakowie,
W DRUKARNI UNIWERSYTETU JAGIELLOŃSKIEGO
pod zarządem Ignacego Stolela.
1877.

History of pediatrics in Lesser Poland

From the report of k.k. State Health Council on health status in Galicja in **1876**:

„In addition to other natural disasters in many places the population of children is decreasing and in a few years time there will be no young people able to be recruited to the army from there."

In **1897** hospital had 72 beds; a hospital headmaster was Maciej Leon Jakubowski. That was the third pediatric hospital in Poland after St. Sophia Hospital in Lwów and Mikołaj Kopernik Hospital in Warszawa. In hospital started working the first pediatric university clinic in Poland. By the end of XIX c. 24 210 children and 3 286 infants were hosptalized

Maciej Leon Jakubowski

First in Poland wrote postdoctoral lecturing qualification on pediatrics in **1864**

„ In order to bring help to suffering people and to put the knowledge of children's illnesses on the same level as other european uniwersities, we should rapidly and effectively organize city hospital for children"
Maciej Leon Jakubowski, 1863

In **1900** during his first lecture as a rector of Jagiellonian University he said:

„The child, no matter sick or healthy, is not a miniature of the adult, but they distinguish from them to the great extent."

In **1889** departament of infants and newborns started working in the hospital. That department treated children of the highest mortality rate, particulary because of dysentery. In **1885** dr Maksymilian Rutkowski began treatment of tuberculosis as the first doctor in Poland Misery in Galicja, called „ land of hunger", was responsible for a huge morbility and mortality in St. Ludwik hospital at that time.

The idea to create a Sanatorium as a hospital departament came up among the doctors Julian Zubrzycki, owner and founder of **Spring Bath in Rabka**, proposed the most beneficial contract to the hospital. The first location of Sanatorium in Rabka was the Providance House. On 9th July **1887** the first group of sick boys came to Rabka. The retired professor M.L. Jakubowski during the First World War was a headmaster of the Sanatorium. The Sanatorium changed its location for beautiful lodge house „**Maciejówka**". The buliding was rebuilt, thus it was posiibble to accomodate over 50 children.

In **1904** the Sanatorium increased its bed capacity by 90 in the „St. Joseph House"
In **1938** The Sanatorium became the part of Jagiellonian University.

Two wars instead of happiness and health brought hell to children.
During the Second World War St Ludwik Hospital, under he german management control was called "little concentration camp"

Nikołaj Nikutin, russian soldier, has written:

„A war was and is the most malicious expression of human activity, because it gets all the worse and infamous out of people. Killing others not only is unpunished but often rewarded. It is allowed to destroy material assets, masterpices which human population has created for centuries. The war changes an ordinary mortal person into tha wild agresor who kills without mercy"

In **1956** the headmaster in Rabka become Prof. **Jan Rudnik** and this center started developing intensively.

In years **1950 - 1960** the center became the leading hospital in Europe in children pulmonary diseases.

In **1956** the ward of bronchial illnesses started working - the first in Poland.

In **1958 dr Jerzy Żebrak**, the father of modern CF therapy in Lesser Poland started working in Rabka.
He recalls his surprise when he found in pediatric textbook from 1953 infant's disease called dysporia entero-broncho-pancreatica familiaris and it was very strange disease for him.
In 70s he was in charge of Cystic Fibrosis and Bronchiology Clinic in Rabka.
He was a co-founder of the Polish Group of CF Treatment.

Patient's recollections:
„It was very tough time. As I remember we often walked to other houses of Institute on medical surveys.
Sometimes we rode by car: Fiat 125p - Institute ambulance.
But sometimes we had not enought strength to walk and no ambulance.
Then dr Żebrak picked us, semi-conscious, up and carried for many hundred metres.
It was quite tiresome in the mountains.
And asked why he breathed so heavily (in polish: sapie) he would answer: because I am homo sapiens."

Scientific work of dr. Żebrak

Płukanie oskrzeli Mistabronem w leczeniu zmian oskrzelowo-płucnych w przebiegu zwłóknienia torbielowatego.
Żebrak J., Werys R., 1979

The Local Immune Status in Cystic Fibrosis
Pryjma J., Rudnik J., Żebrak J., Herman T.: Monogr. Paediat. Karger, Basel, 1979, 125

Echec de la mesure des volumes statiques pulmonaires au cours de la mucoviscidose
Hałuszka J, Żebrak J., Revue Maladie Respiratoire 1984

Środowiskowe zróżnicowanie stanu rozwoju dzieci i młodzieży chorych na mukowiscydozę
Łuszak B, Grabowska J., Żebrak J., Pediatria Polska 1992

Results of CF newborn screening

year	verificated newborn	CF diagnosed
2009	61	7
2010	54	11
2011	58	9
2012	49	7
2013	42	7
2014	39	4
2015	38	5
2016	46	10

CF frequency in the Lesser Poland, Podkarpackie and Świętokrzyskie voivodships 1 : 8 407

THE DEVELOPEMENT OF LUNG TRANSPLANTATION PROGRAM IN SZCZECIN POLAND

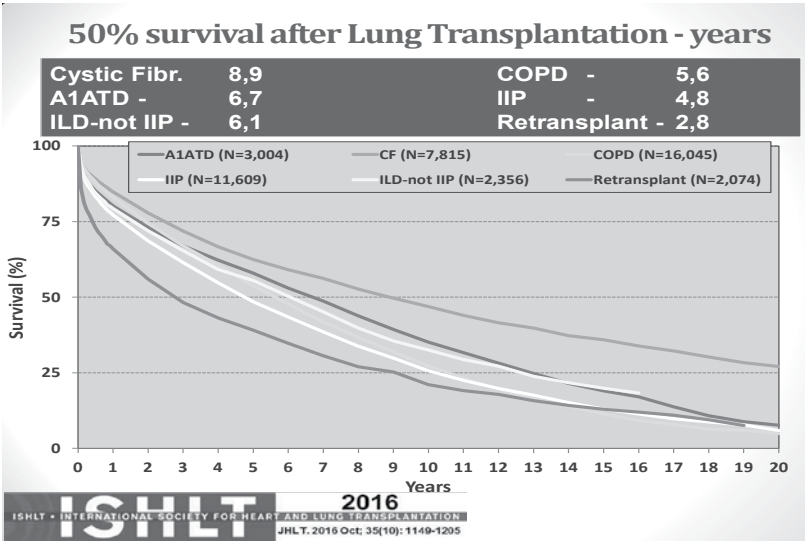
KUBISA Bartosz dr hab.
Director of Lung Transplantation Program Thoracic Surgery and Transplantation Department
Pomeranian Medical University of SZCZECIN, POLAND

Lung Transplantation LuTx - indications

- Chronic respiratory insufficiency resistant to conventional treatment
- Life expectancy below 2 years (CF – 5 years)
- **PaO_2 < 60mmHg in arterial Blood Gas Analysis**
- Progressive cachexia – accelerated qualification to LuTx

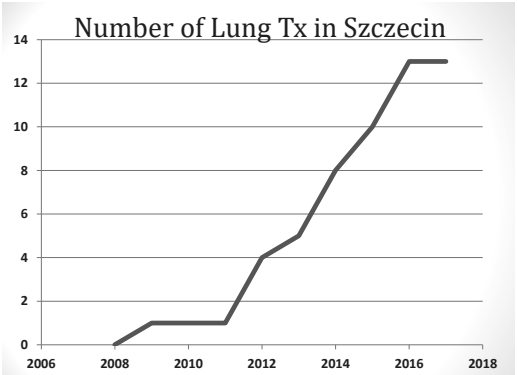
Pomorski Uniwersytet Medyczny w Szczecinie

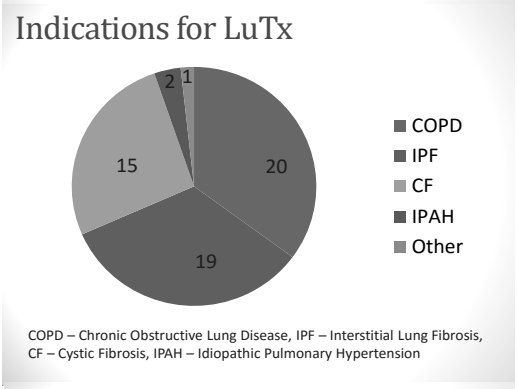
SAMODZIELNY PUBLICZNY WOJEWÓDZKI SZPITAL ZESPOLONY w Szczecinie



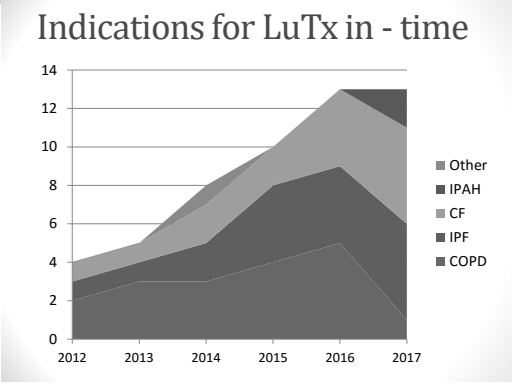
Statistics of LuTx 1996 - 2017 in Szczecin

- 57 transplantations
- 56 patients (1 retransplantation)
- 37 alive
- First successful LuTx in 2011
- 60 pts evaluated for LuTx now
- 20 pts on active waiting list!





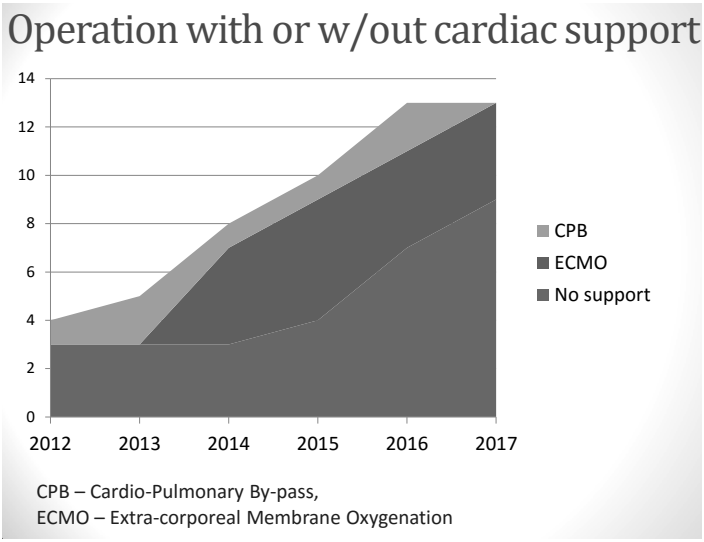
COPD – Chronic Obstructive Lung Disease, IPF – Interstitial Lung Fibrosis, CF – Cystic Fibrosis, IPAH – Idiopathic Pulmonary Hypertension

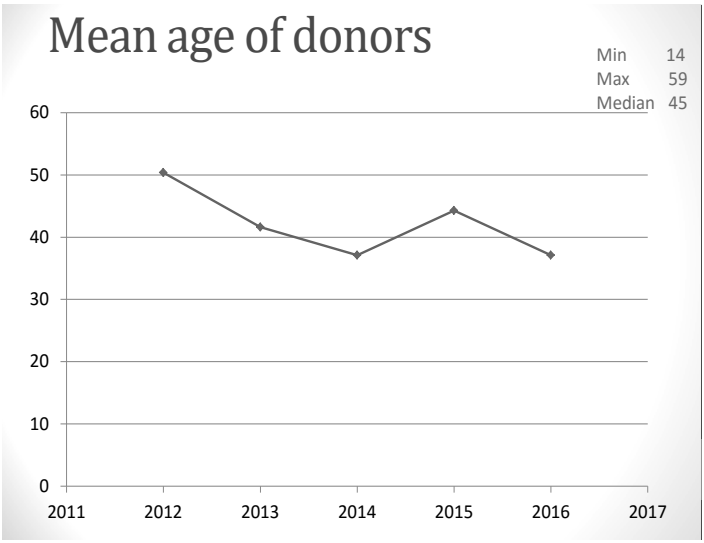


When single or double LuTx?

Single
- Older patient > 60 years
- COPD, IPF
- Comorbidities
- Less perioperative risk
- Worse longrun outlook
- Less experienced center

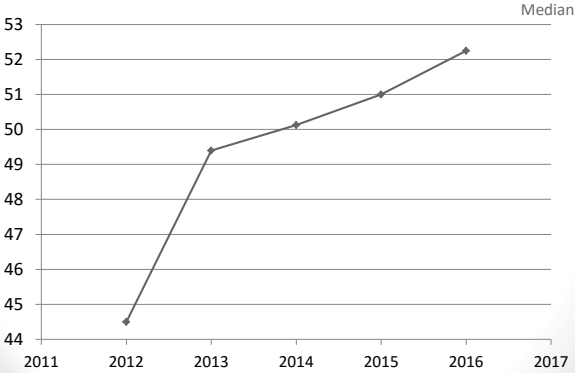
Double
- Younger patient < 60 years
- CF, IPAH
- No comorbidities
- More perioperative risk
- Better longrun outlook
- More experienced center



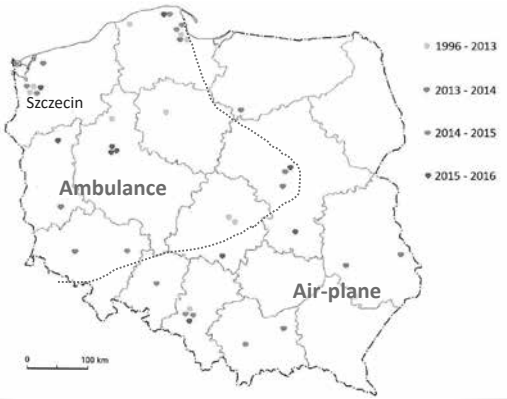


Mean age of recipients

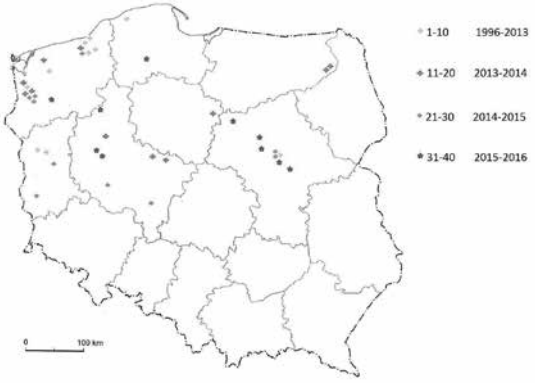
Min	18
Max	64
Median	56



Lung donors for Szczecin



Lung recipients for Szczecin



We always perform real Cross-Match*

- No risk of super acute rejection
- We test minimum two recipients to reduce the risk of two positive results
- Sometimes two recipients are called for the sake of time
- *real Cross-Match – incubation of donor lymphocytes with recipient plasma. Positive result: recipient has circulating Ab against HLA Ag of recipient
- Ab – Antibody, Ag – Antigen, HLA – Human Leukocyte Antigen

Blood group

Poland: blood group distribution

A 40%
0 30%
B 20%
AB 10%

Percent of matching recipients:

For group „0" – 30% matching
For group „B" – 50% matching
For group „A" – 70% matching
For group „AB" – 100% matching

Unfavourable factors for LuTx recipient

Hight < 165cm
Blood group „0"
PRA* > 10
Longer Waiting Time for LuTx! These recipients should be listed earlier.

PRA – Panel Reactive Antibodies

„Compliance" - good feature of recipient

- Ability to co-work
- Subordination
- Good verbal communication
- Ability to risk the operation
- Family support
- How to travel to LuTx center?
- Quit smoking, restrain from piercing, tatoo

Realative contraindications

- Unhealed teeth
- Unverified dermatological changes
- Active smoking – 6 months break in LuTx qualifying
- Tatoo, piercing by men – MSSA? Unhealthy life style?
- Bad sanitary home conditions
- Hepatitis C

Absolute contraindications

- Neoplastic disease – 5 years break
- HIV
- Other organ insufficiency: kidney, liver, heart
- Ev. double organ transplantation to be considered
- Already one organ failure qualifies for double organ Tx. If we wait until two organs failure – the patient may not survive.

Why to disqualify from LuTx by other organ failure?
The LuTx transplanted patient may die due to:

- Kidney insufficiency
- Myocardial infarction
- Unstabilised diabetes mellitus
- Osteoporosis
- Liver insufficiency

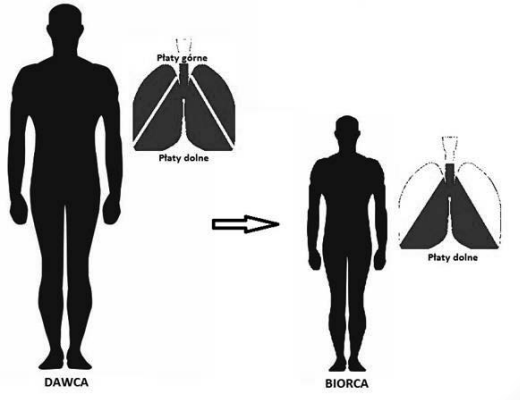
For the public, the fact of death after LuTx is crucial, not the cause:

- Lungs were transplanted,
- The patient has died,
- The lungs were poorly transplanted! - wrong thinking!

Our latest success!

Graft size reduction to transplant lower lobes of big donor in place of whole lungs of small recipient.

Big donor, M 183cm Small recipient, F 151cm



Conclusions

- **Accumulated recipient risk factors - disqualification**
- **Older recipient with COPD and IPF – single LuTx**
- **Younger recipient or with CF – double LuTx**
- **Angiosclerosis, CAD - disqualification**
- **Blood group 0, height < 165cm – earlier qualification**
- **To work on patients' compliance or disqualify uncompliant lung recipient**
- **Recipients from more than 400km – move closer to Lung Tx center – Szczecin!**

ADULT CF PATIENTS – CURRENT SITUATION IN POLAND

SKORUPA Wojciech
Institute of TB and Lung Diseases WARSAW, POLAND

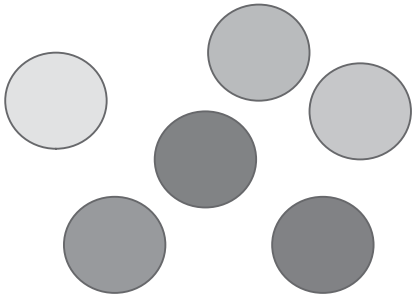
How many adult CF patients live in Poland... ?

About 35% of CF population... probably.

What does an „adult CF center" mean in Poland ?

Two biggest centers are in Warsaw and Poznań (about 120 and 100 patients respectively). Białystok – 23 patients Lublin – 9 patients Sosnowiec, Łódź, Gdańsk, Bydgoszcz, Szczecin...
Many adult patients are still treated in pediatric centers.

Multidisciplinary team…



… and consultants.

Home i.v. antibiotic therapy…

- According to the Polish law intravenous infusion can be done by a qualified nurse or a physician.
- The CF center in Poznań started home i.v. therapy.

Antibiotics in nebulisation

- Colomycin
- high concentrated tobramycin (only for patients with colomycin intolerance or infected with Pa resistant to colomycin)

We need people who want and can…

ADULT CF CENTER IN BUDAPEST

HALÁSZ Adrien, MD, PhD
National Koranyi Institute of Pulmonology, Department of Cystic Fibrosis, BUDAPEST, HUNGARY

Number of adult CF Patients in CF Center: 134 (2017)

Members of the CF team:
physicians
physiotherapists
nurses
psychologist
dietitian
CF coordinator
social worker

Objectives of adult CFcare: Support quality of life and independence of CF patients
health care
psychological support
social assistance

Transition from the paediatric CF center
consultation with the paediatricians
written patient's report
first medical outpatient check up in the adult center

Healthcare

Quarterly check-up:
history - complaints, apetite, fever, quantity and color of the sputum
physical activity, physical examination
BMI
spirometry, O2 saturation, blood gas values
laboratory tests (haemtology, LFTs, PFTs, RFTs, glucose, ions)
sputum bacterial examination
drug treatment control
physiotherapy control
psychologist and dietitian if needed

Yearly check-up:
CT – lung, abdomen, paranasal sinuses
USG – abdomen
cardiology
OGTT
6 MWT
NTMB culture
dietitian

Psychological support:

problems of becoming an adult
separation from parents, parental overprotection
self-confidence, low self-esteem, poor body image
independent communication with the CF team
adherence
family planning
be a man – infertility
be a woman – to be pregnant

Social support.

social isolation
increased uncertainity of future
advice for further education
carreer planning
job counceling
social aid
individual support

Lung transplantation of CF in Hungary:

2000 - 2015 in Wien

adults: **50** (1 lung + heart, 1 lung + liver)
children: **18**

2016 - 2017 in Budapest

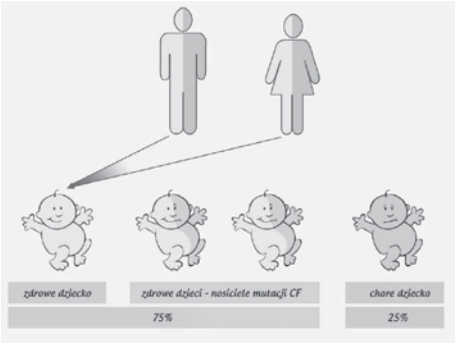
lung tx: **9** (lung+kidney n:1)
presently on the waiting list: **3**

In Wien adults lung and liver n: **2,** children n: **2**

GENETICS IN CYSTIC FIBROSIS

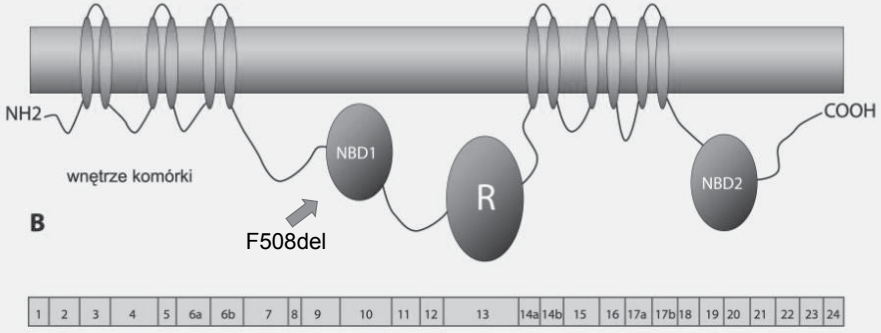
SOBCZYNSKA - TOMASZEWSKA Agnieszka
Centrum Medyczne MEDGEN
Poradnia Genetyczna, Poradnia Dietetyczna, Pracownia Diagnostyki Genetycznej, WARSZAVA, POLAND

W mojej rodzinie nigdy nikt nie chorował…
No one in my family has been affected till now…



Dziedziczenie autosomalne recesywne
Autosomal recessive inheritance

Atypical channel from ABC family



Rycina I-2. *Schemat budowy białka CFTR i mRNA.*
A – schemat budowy i lokalizacji w strukturach komórkowych białka CFTR,
B – schemat budowy mRNA-CFTR z zaznaczonymi eksonami kodującymi odpowiednie domeny białka CFTR,
MSD1 i *MSD2 – domeny transbłonowe,*
NBD1 i *NBD2 – domeny wiążące ATP,*
R – domena regulatorowa

MEDGEN

Sweat test - gold standard ?

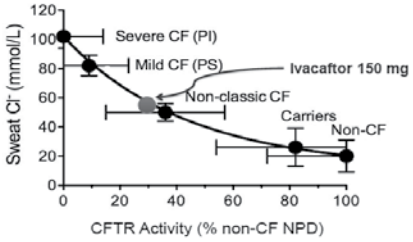
Dzieci i dorośli: do 40 mmol/l	Norma
Noworodki i niemowlęta: do 30 mmol/l	Norma
40-60mmol/l	Szara strefa
powyżej 60 mmol/l	Wynik nieprawidłowy

The correct sweat test does not exclude CF in the presence of clinical symptoms

Prawidłowy wynik testu potowego nie wyklucza rozpoznania CF przy obecności objawów klinicznych

Genotype	Sweat test
F508del/F508del	90-130 mmol/l
	55 mmol/l
F508del/3849+10kbC>T	17-40 mmol/l

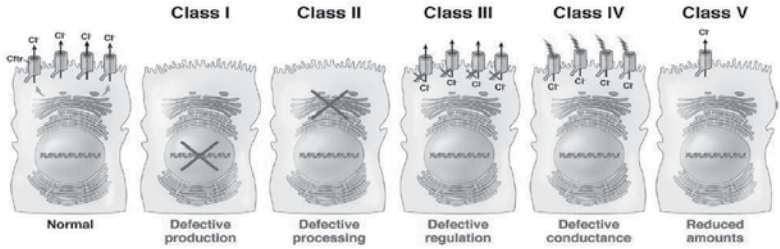
How much CFTR protein do we need?/Ile białka CFTR potrzebujemy?



Adapted from Wilschanski et al., *AJRCCM* 2006 Oct 1;174(7):787-94

~30% CFTR Function → -persistent disease -borderline sweat and NPD

CFTR mutations damage the synthesis, structure, transport to apical membrane, stability and function of the channel



G542X
R553X
W1282X
K710X

F508del
R560T
A561E
R1066C
N1303K

G551D

R334W
R347P

3272-26A>G
3849+10kbC>T

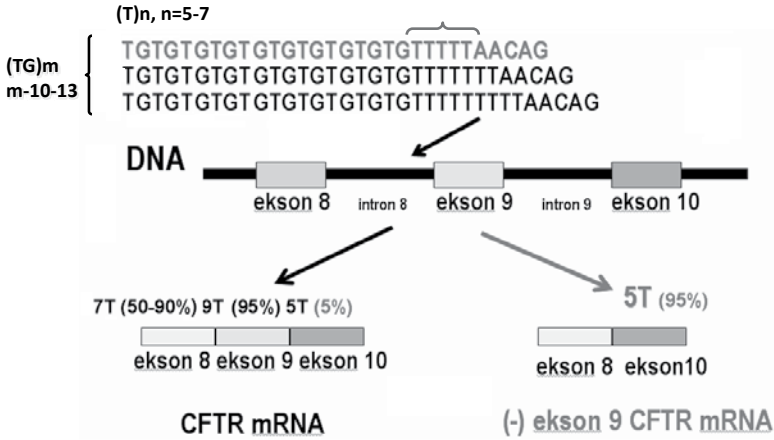
MEDGEN

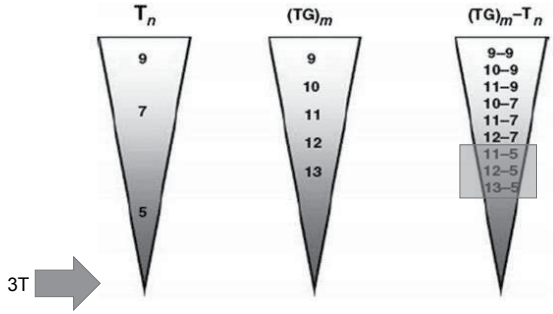
Traditional classification	Class I		Class II	Class III	Class IV	Class V	Class VI
Proposed classification	Class IA	Class IB	Class II	Class III	Class IV	Class V	Class VI
De Boeck and Amaral's classification	Class VII	Class I	Class II	Class III	Class IV	Class V	Class VI
CFTR defect	No mRNA	No protein	No traffic	Impaired gating	Decreased conductance	Less protein	Less stable
Mutation examples	Dele2,3(21 kb), 1717-1G→A	Gly542X, Trp1282X	Phe508del, Asn1303Lys, Ala561Glu	Gly551Asp, Ser549Arg, Gly1349Asp	Arg117His, Arg334Trp, Ala455Glu	3272-26A→G, 3849+10 kg C→T	c. 120del123, rPhe580del
Corrective therapy	Unrescuable	Rescue synthesis	Rescue traffic	Restore channel activity	Restore channel activity	Correct splicing	Promote stability
Drugs (approved)	Bypass therapies (no)	Read-through compounds (no)	Correctors (yes)	Potentiators (yes)	Potentiators (no)	Antisense oligonucleotides, correctors, potentiators? (no)	Stabilisers (no)
Clinical features (global aspect)	More-severe disease				Less-severe disease		

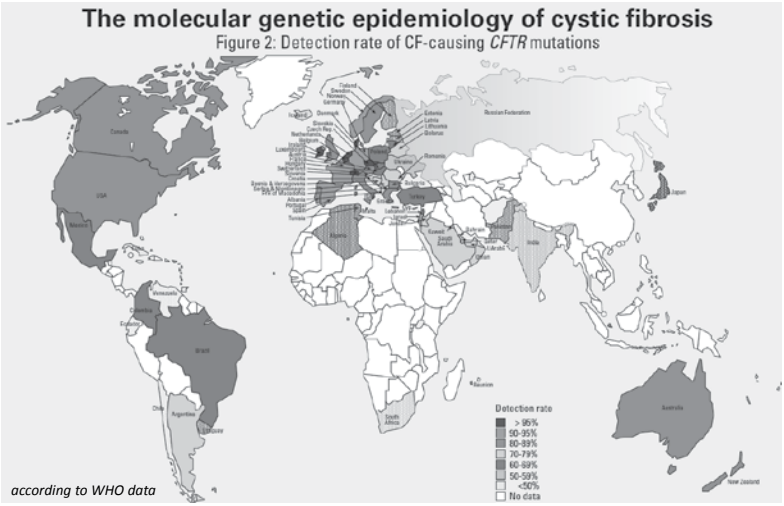
The Lancet Respiratory Medicine 2016 4, e37-e38DOI: (10.1016/S2213-2600(16)30188-6)

CF recommendations/Rekomendacje CF [2008]	**CFTR2**
CF causing mutations, disease causing mutations / mutacje patogenne, odpowiedzialne za CF	
CFTR-related mutations/mutacje odpowiedzialne za choroby CFTR-zależne	Variable consequence mutations/ mutacje o różnym znaczeniu klinicznym
Non causing mutations, non pathogenic mutation/ mutacje niepowodujące CF, bez znaczenia klinicznego	
Mutations of unknown clinical significance / mutacje o nieznanym efekcie klinicznym (zbyt mało danych klinicznych i eksperymentalnych do oceny znaczenia mutacji)	

IVS8-(T)n(TG)m







Mutacje słowiańskie/Slavic mutations

CFTRdele2,3(21kb), 2184insA

Latvia
CF incidence: 1:3300 (from pilot NBS: 1:3520, panel of 230 mutations)
F508del: 61%, dele2,3: 3,2%

Hungary
I stage: 86,25% (30 mutations),
F508del: 70%, dele2,3 – 5%, 2184insA – 5%

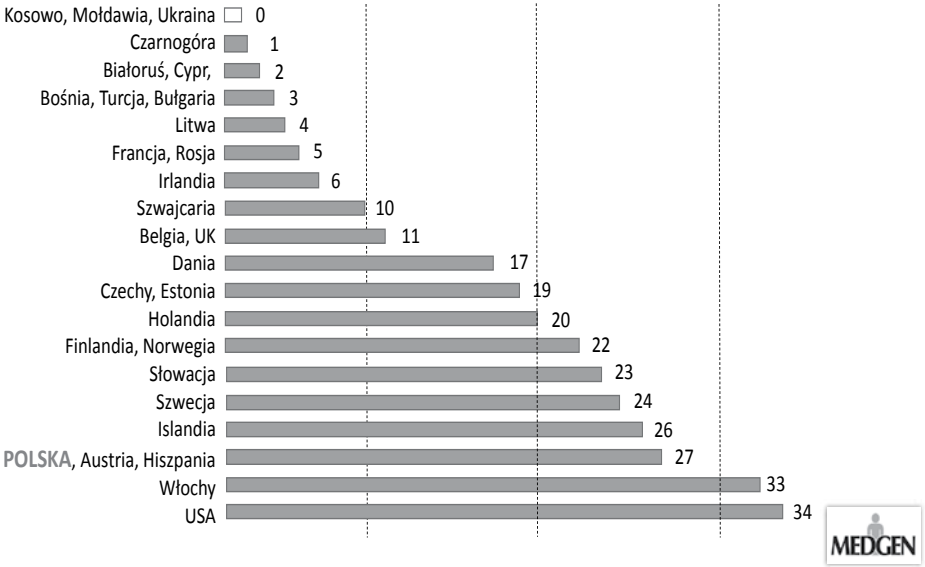
Ukraine
I stage (home made method): 83,7%
CF incidence: 1:3300)
F508del:54,2%,dele2,3(21kb):4,2%,
2184insA: 7,2%

Slovakia
I stage: 86,5% (29 mutations)
incidence (from NBS): 1:6000-7000
F508del: 60.36%,

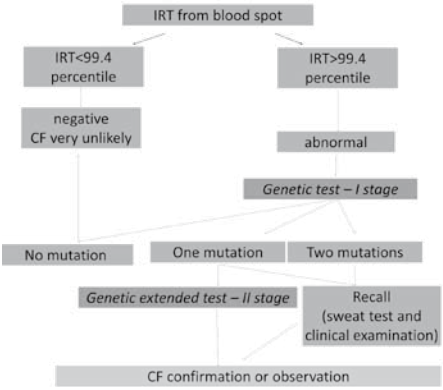
Czech
I stage: 90,7% (29 mutations),
CF incidence 1: 2700 (from NBS 1:4023)
F508del: 67,4%; dele2,3: 5,7%, 2184insA: 0,4%

Poland
I stage: 87% (16 frequent mutations and sequencing)
F508del: 56%, dele2,3(21kb) – 4,4%, 2184insA – 1,5%
CF incidence: 1:2500 (from NBS: 1:4400)

NUMBER OF DISEASES in NBS PROGRAMME



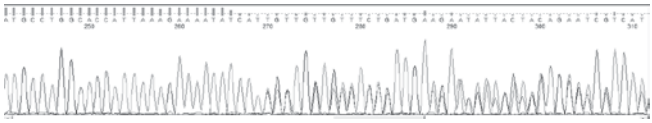
Metabolic error	ID according to MIM	Gene	Inheritance	Number of exons	Hotspot mutations
Phenylketonuria	612349	PAH	AR	13	**p.R158Q, p.R408W, c.1315+1G>A, c.1066-11G>A**
Maple syrup urine disease	248600	BCKDHA BCKDHB DBT DLD	AR	9 10 11 14	No mutation
homocystinuria	236200	CBS	AR	23	**p.I278T**
Hypermethioninemia	250850	MAT1A	AR/AD	9	No mutation
citrulinemia typ II neonatal	605814	SLC25A13	AR	18	No mutation
LCHAD	609016	HADHA	AR	20	**p.E510Q (inna nazwa to p.E474Q)**
VLCAD	201475	ACADVL	AR	20	No mutation
MCAD/ACADM	201450	MCAD/ACADM	AR	12	**p.K329E (inna nazwa p.K304E)**
OTC	311250	OTC	Sprzężone z chr. X	10	No mutation, high frequency
MMA	251000	MUT	AR	13	No mutation
CPT-I	255120	CPT1A	AR	20	No mutation
CPT-II	600650	CPT2	AR	5	No mutation
3-Methylcrotonyl-CoA carboxylase 1 deficiency	210200 210210	MCCC1 MCCC2	AR	19 17	No mutation
HMG-CoA lyase deficiency	246450	HMGCL	AR	9	No mutation
Isovaleric aciduria	243500	IVD	AR	12	**p.Ala314Val**
Glutaricaciduria, type I/ kwasica glutarowa I	231670	GCDH	AR	11	No mutation
tyrosinemia typ I	276700	FAH	AR	14	**IVS6-1G>T**



Eur J Hum Genet. 2013 Apr;21(4):391-6. doi: 10.1038/ejhg.2012.180. Epub 2012 Aug 15.
Newborn screening for cystic fibrosis: Polish 4 years' experience with CFTR sequencing strategy.
Sobczyńska-Tomaszewska A[1], Oltarzewski M, Czerska K, Wertheim-Tysarowska K, Sands D, Walkowiak J, Bal J, Mazurczak T; NBS CF working group.

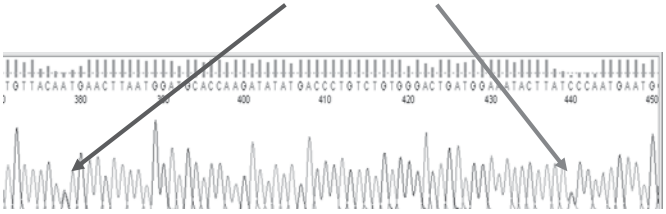
CF częstość/CF incidence: 1/4400
CF nosicielstwo/CF carrier: 1/33

POSZUKIWANIE MUTACJI RZADKICH, ULTRARZADKICH i DE NOVO
SEARCHING FOR RARE, ULTRARARE and DE NOVO MUTATIONS



SANGER SEQUENCING: method sensitivity 99,9%

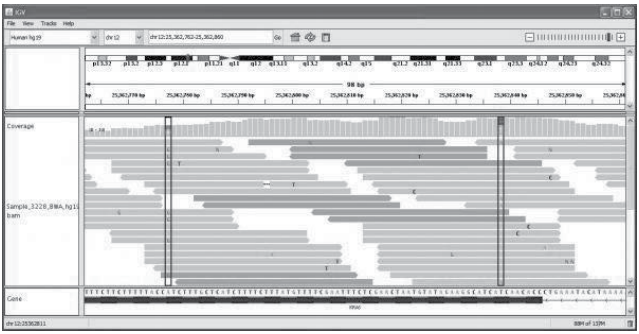
Allows to detect both frequent and rare mutations



SEARCHING FOR RARE, ULTRARARE AND DE NOVO MUTATION

MEDGEN

NEXT GENERATION SEQUENCING/SEKWENCJONOWANIE NOWEJ GENERACJI (NGS)



L.p.	Mutacja	Lokalizacja (wg tradycyjnej numeracji eksonów CFTR)	Częstość (%)	Obecność w bazach
1	F508del*	10	56,8	CFTR1, CFTR2
2	dele2,3(21kb)*	2,3	4,4	CFTR1, CFTR2
3	3849+10kbC>T*	intron19	3,5	CFTR1, CFTR2
4	G542X*	11	2,9	CFTR1, CFTR2
5	F1052Val	17b	2,8	CFTR1, CFTR2
6	N1303K*	21	2,2	CFTR1, CFTR2
7	R553X*	11	1,7	CFTR1, CFTR2
8	2184insA*	13	1,5	CFTR1, CFTR2
9	D1152H	18	1,3	CFTR1, CFTR2
10	2143delT*	13	1,2	CFTR1, CFTR2
11	1717-1G>A*	7	1,1	CFTR1, CFTR2
12	R347P*	7	1,0	CFTR1, CFTR2
13	W1282X*	20	1,0	CFTR1, CFTR2
14	P750L	13	0,9	CFTR1
15	R297Q	7	0,9	CFTR1
16	3272-26A>G*	Intron 16	0,8	CFTR1, CFTR2
17	R117H*;**	4	0,8	CFTR1, CFTR2
18	2183AA>G*	13	0,6	CFTR1, CFTR2
19	D806G	13	0,5	CFTR1
20	K710X	13	0,5	CFTR1, CFTR2
21	L671X	7	0,5	---
22	R334W*	17b	0,5	CFTR1, CFTR2
23	G1069R	7	0,4	CFTR1, CFTR2
24	Y301C	7	0,3	CFTR1
25	R352W	13	0,3	CFTR1
26	Q685TfsX4	18	0,2	---
27	3600+2insT	intron 17b	0,2	CFTR1, CFTR2
28	Y1092X	7	0,2	CFTR1, CFTR2
29	I336K	10	0,2	CFTR1, CFTR2
30	T582I	17b	0,2	CFTR1
31	T1057A	4	0,2	CFTR1
32	R153K	7	0,2	---
33	T351S	17b	0,2	CFTR1
34	I1051Val	17b	0,2	CFTR1
35	R1102X	7	0,2	CFTR1, CFTR2
36	M348K	10	0,2	CFTR1

Summary of data from
- CM MedGen
- Screening Department, Institute Mother and Child

MEDGEN

Diagnostic dilemma…

abnormal screening tests (elevated IRT) + inconclusive sweat tests and/or DNA results

CRMS (CFTR related metabolic syndrome) in the USA
Cystic Fibrosis Screen Positive, Inconclusive Diagnosis in Europe

The definition of CRMS/CFSPID concerns an infant with a positive NBS test for CF and either:
• A sweat chloride <30 mmol/L and 2 *CFTR* mutations, at least 1 of which has unclear phenotypic consequences *OR*
• An intermediate sweat chloride value (30-59 mmol/L) and 1 or 0 CF-causing mutations

ICD-9: 277.9, ICD-10: E88.9: : niespecyficzna choroba metaboliczna /nonspecific metabolic diesease/

17% of newborn in USA registry after NBS have diagnosed CRMS

F508del/R117H is the most frequent genotype among CRMS patients

CRMS/SPID – one year clinical observation is necessary

Diagnosis of Cystic Fibrosis in Screened Populations

Philip M. Farrell, MD, PhD[1], Terry B. White, PhD[2], Michelle S. Howenstine, MD[3], Anne Munck, MD[4], Richard B. Parad, MD, MPH[5], Margaret Rosenfeld, MD, MPH[6], Olaf Sommerburg, MD[7], Frank J. Accurso, MD[8], Jane C. Davies, MBChB, FRCPCH, MD[9], Michael J. Rock, MD[1], Don B. Sanders, MD, MS[10], Michael Wilschanski, MBBS[11], Isabelle Sermet-Gaudelus, MD, PhD[12], Hannah Blau, MBBS[13], Silvia Gartner, MD[14], and Susanna A. McColley, MD[15]

Objective Cystic fibrosis (CF) can be difficult to diagnose, even when newborn screening (NBS) tests yield positive results. This challenge is exacerbated by the multitude of NBS protocols, misunderstandings about screening vs diagnostic tests, and the lack of guidelines for presumptive diagnoses. There is also confusion regarding the designation of age at diagnosis.

Study design To improve diagnosis and achieve standardization in definitions worldwide, the CF Foundation convened a committee of 32 experts with a mission to develop clear and actionable consensus guidelines on diagnosis of CF with an emphasis on screened populations, especially the newborn population. A comprehensive literature review was performed with emphasis on relevant articles published during the past decade.

Results After reviewing the common screening protocols and outcome scenarios, 14 of 27 consensus statements were drafted that apply to screened populations. These were approved by 80% or more of the participants.

Conclusions It is recommended that all diagnoses be established by demonstrating dysfunction of the CF transmembrane conductance regulator (CFTR) channel, initially with a sweat chloride test and, when needed, potentially with newer methods assessing membrane transport directly, such as intestinal current measurements. Even in babies with 2 CF-causing mutations detected via NBS, diagnosis must be confirmed by demonstrating CFTR dysfunction. The committee also recommends that the latest classifications identified in the Clinical and Functional Translation of CFTR project [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis. Finally, to avoid delays in treatment, we provide guidelines for presumptive diagnoses and recommend how to determine the age of diagnosis. *(J Pediatr 2017;181S:S33-44).*

Mutation status is not fixed

CFTR2 Clinical and Functional Translation of CFTR

Variant cDNA name (ordered 5' to 3')	Variant protein name	Variant legacy name	dbSNP rsID, if available	# alleles in CFTR2	Allele frequency in CFTR2 (of 141,340 identified variants)*	% pancreatic insufficient (patients with variant in trans with ACMG-PI variant)	Variant final determination 3 March 2017 (current version)	Change from previous version?
c.92G>T	p.Arg31Leu	R31L	rs149353983	7	0,00005	0%	Unknown significance	Yes
c.509G>A	p.Arg170His	R170H	rs1800079	11	0,00008	33%	Unknown significance	Yes
c.601G>A	p.Val201Met	V201M	rs138338446	11	0,00008	25%	Unknown significance	Yes
c.1327G>T	p.Asp443Tyr	D443Y	rs147422190	8	0,00006	25%	Varying clinical consequence	Yes
c.1584+1G>A	No protein name	1716+1G->A	rs397508230	5	0,00004	50%	CF-causing	Yes
c.1680-877G>T	No protein name	1811+1643G->T	rs397508261	26	0,00018	100%	CF-causing	Yes
c.1684G>A	p.Val562Ile	V562I	rs1800097	20	0,00014	43%	Unknown significance	Yes
c.1763A>T	p.Glu588Val	E588V	rs397508297	6	0,00004	50%	Varying clinical consequence	Yes
c.1766+5G>T	No protein name	1898+5G->T	rs121908796	6	0,00004	80%	CF-causing	Yes
c.2506G>T	p.Asp836Tyr	D836Y	rs201386642	9	0,00006	50%	Unknown significance	Yes
c.3468G>A	No protein name	3600G->A	rs139729994	15	0,00011	38%	CF-causing	Yes
c.3468+2_3468+3insT	No protein name	3600+2insT	not found	12	0,00008	100%	CF-causing	Yes
c.3468+5G>A	No protein name	3600+5G->A	not found	3	0,00002	33%	CF-causing	Yes
c.3717G>A	No protein name	3849G->A	rs144781064	3	0,00002	67%	CF-causing	Yes
c.3717+40A>G	No protein name	3849+40A->G	rs397508595	13	0,00009	30%	CF-causing	Yes
c.3873+2T>C	No protein name	4005+2T->C	rs146795445	15	0,00011	27%	CF-causing	Yes

Orkambi™ (lumacaftor + ivacaftor)

Overview | Clinical Trials | News

Description
Orkambi™ (also known as lumacaftor/ivacaftor) is a new therapy combining lumicaftor a "corector", designed to move defective CFTR protein to the proper place in the airway cell membrane, with the "potentiator" ivacaftor that improves function of CFTR as a chloride channel.

Therapeutic Approach
CFTR Modulation

Status
The FDA has approved the use of Orkambi™ in people with CF who have two copies of the F508del CFTR mutation and are 12 years and older. A phase three trial is being conducted in children ages 6-11 who have two copies of the F508del CFTR mutation.

Phase
To Patients

Sponsor
The program is sponsored by Vertex Pharmaceuticals, Inc. and partially funded by Cystic Fibrosis Foundation Therapeutics.

Recent Changes

07/02/2015
Orkambi™ was approved by the FDA for people with CF who have two copies of the F508del CFTR mutation and are 12 years and older.

Kalydeco™ (also known as ivacaftor)

Overview | Clinical Trials | News

Description
Kalydeco™ (previously known as VX-770) is a new oral medication that was approved by the FDA on January 31, 2012 for people with CF ages 6 and older with the G551D mutation of CF. It is the first drug available that targets the underlying cause of CF – a faulty gene and its protein product, CFTR.

Therapeutic Approach
CFTR Modulation

Status
Phase 3 trials have been completed in pediatric and adult people with CF who have one copy of the G551D mutation in their CF gene. There were no safety issues in these trials and the treatment groups met the primary endpoint for improved lung function and secondary endpoints of reduced pulmonary exacerbations, increase in weight, and increase in quality of life measures.

The FDA has approved the expanded use of Kalydeco™ for people with the following cystic fibrosis gene mutations: G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D and R117H.

Phase
To Patients

Sponsor
The drug was developed by Vertex Pharmaceuticals, Inc. with significant scientific, clinical and financial support from the Cystic Fibrosis Foundation.

Recent Changes

03/18/2015
The FDA has approved the use of Kalydeco™ (ivacaftor) in children ages 2-5 with certain CFTR mutations.

DAMAGE TO THE LIVER AND BILE DUCTS IN CYSTIC FIBROSIS WITH REGARD TO LIVER AND PANCREAS TRANSPLANTATION

WIĘCEK Sabina
Department of Paediatrics, Medical University of Silesia, KATOWICE, POLAND

Etiopathogenesis of hepatic lesions:
a combination of complex processes of fibrosis, inflammation, re-modelling, apoptosis and cholestasis, a consequence of the abnormal functioning of the CFTR protein, immunologic reactions and response to oxidative stress

Patophysiological changes to the bile acids in the course of cystic fibrosis

1. Changes to the components of the bile (abnormal water and electrolyte contents and change to the pH of the bile)
2. Changes to the profile of bile acids – to hydrophobic
3. Abnormal transportation of the bile
4. Retention of toxic bile acids (taurocholic acid)
5. Induction of pro-inflammatory chemokines -> biliary fibrogenesis

Pereira T. et all . J.Pediatr.Gastroenterol.Nutr. 2012;3:328-335.

Factors contributing to the processes of precipitation of bile acids in the bile ducts:

- Decreased synthesis of the salts of the bile acids
- Decreased absorption of bile acids from the lumen of the small intestine
- Narrowing of the bile ducts impairing the outflow of the bile from the liver to the lumen of the duodenum

Patient 1

- born 27.10.03
- C-V, P-IV, SN, body mass - 3200g, Apgar - 10 points
- 3 yo – hospitalised at the Department of Haematology hepatosplenomegaly, suspected proliferative disease.
- Body mass - 25-50pcn, Height - 25-50pcn
- Sporadic upper respiratory tract infections
- Normal stools
- AlAT - 56 U/l, AspAT - 63 U/l, GTP - 112 U/l
- Protein - 83 g/l
- Fatty steatocrit index - 38,5%
- Abdominal ultrasound- connective tissue penetrates through the portal system and divides the hepatic parenchyma into multiple “nodes”. Winding portal vein.
- Sweat test - Cl-98mmol/l
- Genetic test - F508del/F508del

The following were excluded - Viral hepatitis, alpha-1 antitrypsin deficiency, Wilson’s disease, AIH, coeliac disease

Patient 1
2013
- Sporadic cough reported in the anamnesis,
- Hb - 9,8g%, RBC-4050000, WBC - 1700, PLT - 65000
- INR - 1,44, AlAT- 39 U/l, AspAT - 47 U/l, GTP - 44 U/l
- Doppler ultrasound - enlarged liver, entirely covered in lumps, with irregular borders. Nar rowing of the hepatic veins, non-dilated portal vein with a slow flow. A large number of hyperechogenic fibrous tissues. Significantly en larged spleen.
- Panendoscopy - second/third degree oesophageal varices, thickened folds of the fundus of the stomach, features of portal gastropathy

Further treatment, variceal band ligation and referral for liver transplant

GENETIC FACTORS: Type of CFTR mutation
- So far, no specific mutation relating solely to liver damage in the course of cystic fibrosis has been discovered.
- Most commonly, these are the so called „serious mutations" of the CFTR gene (delta F508, G524X, N1303K, CFTRdel21kB, 1811+1G-> C).
- The delta 508 mutation plays a particular role in the development of hepatic lesions in the course of cystic fibrosis due to its stimulation of an increased loss of bile acids with stools and the fact that it leads to the formation of more hydrophobic bile acids.

Freudenberg F. et all. Am.J.Gastrointest.Liver Physiol. 2008;294:1411-20

GENETIC FACTORS: the 1 Serpina gene
- It occurs in about 2% of the patients with cystic fibrosis and in about 5% of the patients with cystic fibrosis and co-occuring hepatic lesions.
- Responsible for the synthesis of the inhibitor of serine protease. The protein connected to allele Z is concentrated within the endoplasmic reticulum of hepatocytes leading to their damage, inflammation and cirrhosis.
- In about 10% of allele Z homozygotes, accumulation of the SERPINA gene protein leads to neonatal hepatitis and in 2-3% of cases, to fibrosis and cirrhosis.
- A high risk of portal hypertension in patients with present allele Z of the SERPINA gene has been confirmed.
- Its occurence is linked to the risk of the development of chronic obstructive pulmonary disease.

Bartlett J. et all. JAMA 2009;9:1076-83.

GENETIC FACTORS
- Gene of plasminogen activator inhibitor type 1 (PAI1)
- Genes relating to metalloproteinases (TIMP)
- P1 glutation s-transferase gene (GSTP1)
- Transforming growth factor beta gene (TGF-B1)
- Uridilyltransferase gene (UGT1A1)

IMMUNOLOGICAL FACTORS
ROLE OF CHEMOKINES - activation of stellate cells. (source : hepatic macrophages, endothelial cells, bile duct epithelial cells, lymphocytes, blood platelets and hepatocytes)
- Monocyte chemotactic protein (MCP1)
- Macrophage inflammatory protein beta 1 (MIP1B)

- TGF-beta
- TNF-alfa
- Platelet-derived growth factor (PDGF)
- Interleukins – IL-1,IL-6, IL-10

Abnormalities of cholangiocytes ↓
Mucous plugs in bile ducts ↓
Inflammatory and proliferative processes ↓
Focal biliary fibrosis (25-30%) ↓
Multilobular biliary cirrhosis (10%) ↓
Portal hypertension ↓
Hepatic insufficiency ↓
Chart 1. Patogenesis of hepatic lesions the course of cystic fibrosis according to Colombo.

Colombo C. et all. J.Pediatr.Gastroenterol.Nutr. 2006;43:49-55.

Organ lesions contributing to the manifestation of CFLD

- The presence of hepatic lesions (CFLD- cystic fibrosis liver damage) was concluded in 28% (80/288) of CF patients.
- The symptoms of CFLD occured as the patient aged.
- All patients with hepatic lesions were diagnosed with pancreatic insufficiency.
- No correlation between the occurence of hepatic lesions and pulmonary lesions, respiratory insufficiency, the level of malnutrition, meconium ileus and/or DIOS (distal intestinal obstruction syndrome) was concluded. *Wilschanski M. Paediatrics 1999,103,52-7.*
- *Lindblad* observed meconium ileus in only 12% of CF patients, out of whom only 6/15 patients with meconium ileus had the symptoms of liver damage. (Hepatology 1999;5:1151-1158)
- *Siano* did not prove the correlation between the occurence of hepatic lesions in the course of cystic fibrosis and the pancreatic efficiency and the level of nutrition. In 2-5% of patients, focal biliary cirrhosis develops into multilobular cirrhosis *(Dig.Liver Dis. 2010;42:428-431).*
- Risk factors - male gender (a probable protective role of oestrogens in women).

The role of undernourishment

- Children with diagnosed cystic fibrosis and liver damage have lower body mass, height, circumference of the upper arm and BMI
- Patients with cystic fibrosis also have significantly lower levels of linoleic (LA), docosahexaenoic (DHA) and docosapentaenoic (DPA) acids
- The influence of parenteral nutrition
- The role of antioxidant deficiency
- Vitamin deficiency
- Essential fatty acids deficiency

The role of the hepatoxic effect of medications

- Abnormal functions of oxidases and P450,CYP2C8, CYP2C9, CYP3A4 cytochromes.
- The dose of beta lactame should be reduced by 20%
- The doses of aminoglycosides should be decided upon depending on the level of the medication in the blood serum
- Increased microsomal metabolism relating to theophylline and methylxanthine through the affected 1st phase of the biotransformation of the medications
- Increased hepatic clearance of the 2nd phase, which may be reflected in the abnormal metabolism of furosemide, lorazepam and ibuprofen

Kearns G. et all. Ann.Pharmacother.1993;27:74-79.

Defects of the gall bladder and bile ducts

- In about 30% of patients with cystic fibrosis, atrophic gall bladder or the lack thereof, also its defects and/or of bile ducts is reported.
- No correlation between cirrhosis and abnormalities in the gall bladder and/or bile ducts has been observed.
- Gallbladder hyldrops and lithiasis are significantly statistically more commonly observed in patients with cystic fibrosis compared to the healthy population.
- The narrowing of the distal regions of the bile ducts is frequent and may occur in even 90% of CF patients and contribute to the formation of gallstones.

Cholelithiasis:

- Cholelithiasis concerns 14-24% of CF patients
- The following play a role in the pathogenesis of the formation of gallstones: abnormal bile content, increased excretion of bile acids with stools and the formation of lithogenic bile where bile acids are interlocked with glycine.
- No correlation between the formation of gallstones and supplementation with pancreatic enzymes has been confirmed.

Risk factors of the development of liver diseases in cystic fibrosis

- Male gender – of patients with CFLD are boys. Protective role of oestrogens in women.
- Co-existing meconium ileus (inconsistent data- from a 5-times' higher risk of developing hepatic lesions to a similar risk). Only 25% of patients with CFLD had meconium ileus in the medical interview. Meconium ileus is not a prerequisite for CFLD. Probably, parenteral nutrition is an additional factor.
- Significant undernourishment.
- Pancreatic insufficiency
- Severe genotype (delta F508).

Hepatic lesions in the course of CF

1. Focal hepatic fibrosis 72%
2. Focal biliary cirrhosis 20-30%
3. Multilobular biliary cirrhosis 5-15%
4. Portal hypertension 2-5%
5. Small atrophic gallbladder and narrowing of bile ducts 15-45%
6. Cholelithiasis 14-24%7. Steatosis 25-60%
8. Cholestasis in newborns <10%
9. Primary sclerosing cholangitis rarely

10. Cholangiocarcinoma rarely
11. Drug-induced, toxic liver damage

Clinical symptoms of CFLD
- In most CF patients, the course of hepatic complications is **symptomless.**
- **Pruritus** sometimes occurs and jaundice in patients whose condition is advanced.
- Accidentally diagnosed **hepatomegaly** is usually the first symptom.
- In newborns, **steatosis** may be accidentally discovered in a routine abdominal ultrasound.

Diagnosis of hepatic lesions in the course of cystic fibrosis :
1. CLINICAL SYMPTOMS
- Hepatomegaly, symptoms of portal hypertension
- Very frequent symptomless course

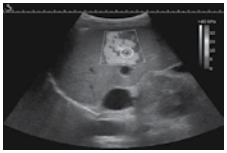
2. Periodic laboratory tests (the levels of AlAT, AspAT, GGTP, bilirubin and bile acids, the APRI index and Fibrotest)
- It is believed that elevated levels of at least 2 hepatic parameters above the norm within at least 3 months is an indication of advancing hepatic lesions.
- Low sensitivity and specificity
- Most patients with multifocal cirrhosis have normal test results. Isolated elevation of aminotransferases with concurrent normal GGTP index may indicate steatosis.

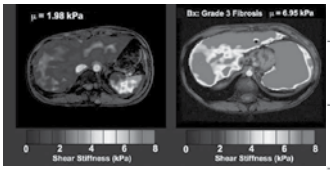
3. Abdominal ultrasound and a Doppler test- assessment of the level os steatosis, symptoms of portal hypertension and cirrhotic transformation of the liver). Inexpensive and non-invasive test. Normal imaging of the liver does not exclude the ongoing process of fibrosis.

4. Liver biopsy with histopathological assessment – apart from being painful, it is invasive, prone to side-effects and sampling errors

5. Non-invasive parameters of liver fibrosis
Fibroindex, amino peptides of type III procollagen, collagen I, collagen IV, laminine, hyaluronic acid, Cytokines and chemokines relating to the process of fibrosis, cytokeratin 18.

Elastography – noninvasive method for the detection of liver disease





Liver fibrosis staging	Metavir score	kPa	m/s
Normal	F0	2.0 – 4.5	.81 – 1.22
Normal – Mild	F0 – F1	4.5 – 5.7	1.22 – 1.37
Mild – Moderate	F2 – F3	5.7 – 12.0	1.37 – 2.00
Moderate – Severe	F3 – F4	12.0 – 21.0+	2.00 – 2.64+

ELSEVIER

Journal of Cystic Fibrosis 16 (2017) 139–145

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

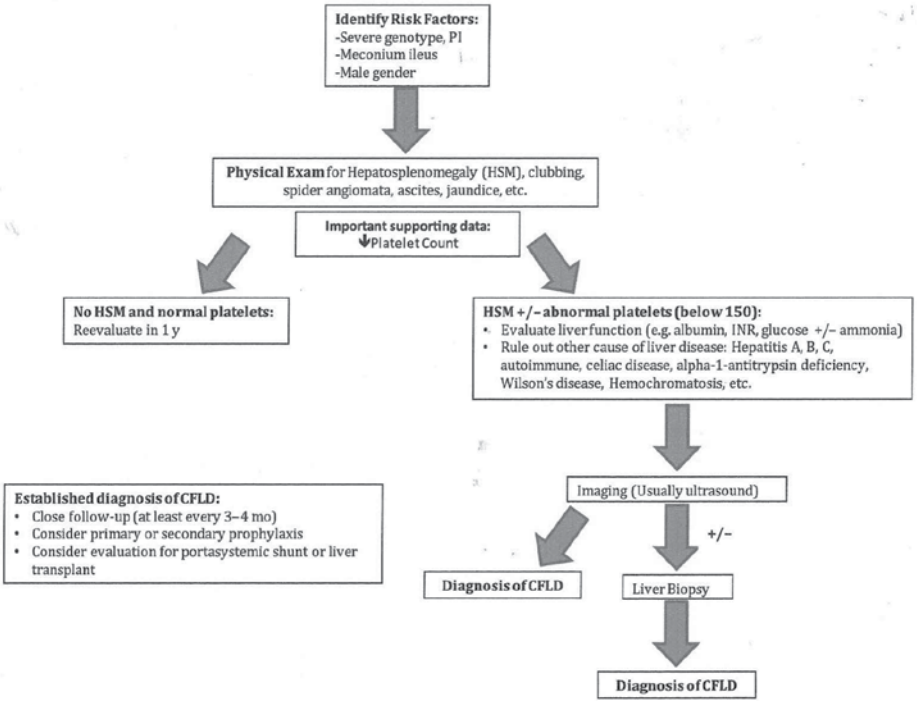
Prevalence of elevated liver enzymes in children with cystic fibrosis diagnosed by newborn screen☆

Samantha A. Woodruff [a], Marci K. Sontag [c], Frank J. Accurso [b], Ronald J. Sokol [a], Michael R. Narkewicz [a,*]

- Elevated liver enzymes are common during childhood in CF patients identified by newborn screen.
- Elevation of liver enzymes above 3X ULN is very unusual at annual visits.
- Elevated AspAT and GTP maybe markers for risk of advanced liver disease.

ALGORITHM FOR DIAGNOSIS , EVALUATION AND MANAGEMENT OF CFLD

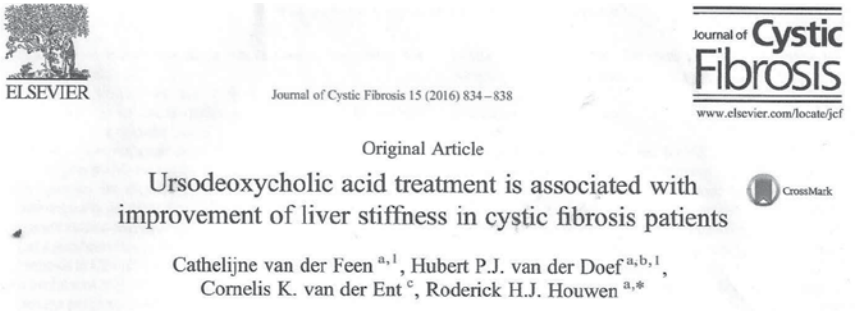
Sathe M, Freeman A. Gastrintestinal, pancreatic and hepatobiliary manifestations of cystic fibrosis. Pediatr Clin N Am 2016;63:679-698.



The treatment of hepatic lesions in cystic fibrosis:

1. Background therapy of cystic fibrosis
2. Diet therapy
   - Prevention of undernourishment in cystic fibrosis.
   - Feeding tube or PEG nutrition recommended.
3. Ursodeoxycholic acid
   - Has cytoprotective effect on the cell membranes of cholangiocytes,
   - Stimulates the secretion of chloride ions through calcium-dependent chloride channel.
   - Reduces the ratio of cholic acid in bile (less than 5%), reduces its synthesis and lowers its overall volume. It also stimulates cholangiocytes and hepatocytes to secrete.
   - Has anti-apoptopic effect and reduces the toxic effects of hydrophobic bile acids.

- There are few trials assessing the effectiveness of ursodeoxycholic acid. There is insufficient evidence to justify its routine use in cystic fibrosis....
- Routine use of UDCA in people with CF cannot, therefore be recommended !!!



ELSEVIER

Journal of Cystic Fibrosis 15 (2016) 834–838

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Original Article

Ursodeoxycholic acid treatment is associated with improvement of liver stiffness in cystic fibrosis patients

CrossMark

Cathelijne van der Feen [a,1], Hubert P.J. van der Doef [a,b,1], Cornelis K. van der Ent [c], Roderick H.J. Houwen [a,*]

- Present data suggesting that UDCA when started before severe liver damage is present, might be able to prevent the progression of CFRLD and might even induce a reversal of fibrosis.

4. The treatment of portal hypertension
   - Beta- blockers
   - Endoscopic methods for the treatment of esophageal varices
5. Liver transplant
   - Advancing dysfunction of the liver, progressing ascites and jaundice, recurrent bleeding from esophageal varices and hepatopulmonary syndrome

European recommendations for the treatment of with cystic fibrosis and hepatic lesions

1. Bio-chemical tests (AlAT, AspAT,GGTP, FA, prothrombin time, blood platelets) every 6 months.
2. Imaging tests – abdominal ultrasound, alternatively annual CT or MR.
3. Ursodeoxycholic acid at 20mg / kg daily with divided doses being more effective.
4. Panendoscopy performed every 2-3 years is necessary in patients with cirrhosis and or splenomegaly in order to exclude esophageal verices.
5. Assessment of the hepatopulmonary syndrome – assessment of intrapulmonary shunts as they intensify hypoxaemia.

6. In the case of cirrhosis – assesment of the levels of alpha-fetoprotein (AFP) every 6 months.
7. Mild esophageal varices – non selective beta blockers ? Levels 2-3 varices – endoscopic treatment or intrahepatic portosystemic shunts.
8. Prevention of undernutrition (via feeding tube or PEG).

Herrmann U. Best Practise &Research Clin.Gastroenterol. 2010;24:585-592.

Recommendations of PTM

- "Regular tests (at least once a year) of basic liver functions (levels of bilirubin, albumines, aminotransferases, the prothrombin ratio and GGTP) and Doppler ultrasound of the abdomen are necessary in the case of cystic fibrosis."
- „Preparations with ursodeoxycholic acid at 10-40mg/kg/24h should be administered to patients with abnormal functions of the liver and bile ducts, and all patients with neona tal cholestasis."
- „Patients with suspected portal hypertension (enlarged pacreas, slowing of the portal vein flow <15cm/sec.) should undergo gastroscopy and optional endoscopic variceal ligation – EVL."
- „Liver transplant should be considered in patients with advanced cirrhosis and portal hypertension."

Indications for liver transplant in children with cystic fibrosis

- Failure of the liver
- Portal hypertension – recurring bleeding from the esophagus (ineffective endoscopic treatment / TIPS)
- Recurring peritonitis
- Hepatocarcinoma • Mean age of patients with CF at transplant who underwent LT was significantly lower than
  in patients with CF that underwent LLT (14.4 vs 20.1)
- More than 90% of the transplanted patients were Caucasian
- Abnormal total bilirubin level was found in 59% of all transplanted patient with CF, signifi cantly more in patients who underwent LLT
- Almost a fifth of LT and LLT patients had diabetes at transplant
  6.7% of the patients had encephalopathy,
  12% had episodes of gastrointestinal bleeding
  59.7% had ascites
- All patients who underwent combined LLT received whole liver compared to 0.1% of the patients who underwent LT
- Retransplantation was performed in 20 (8,7%) LT patients and in no patients receiving a combined LLT.
- No patients with combined LLT underwent liver or lung re-transplantation during the study.
- Patients with isolated LT had significantly higher BMI , higher prevalence of encephalopa thy and diabetes and lower albumin at transplant.

Table 3. Patient outcomes after LT and LLT for CF

	All patients (n = 245)	LT (n = 230)	LLT (n = 15)	p-Value
Graft survival (%)				
1 yr	76.3	76.1	80.0	0.73
5 yr	67.8	67.0	80.0	0.30
Patient survival (%)				
1 yr	83.7	83.9	80.0	0.69
5 yr	75.9	75.7	80.0	0.70
Early graft loss (%)				
≤ 30 days	12.7	12.6	13.3	0.94
≤ 14 days	6.5	6.5	6.7	0.98
Early death (%)				
≤ 30 days	9.0	8.7	13.3	0.54
≤ 14 days	4.5	4.3	6.7	0.67

Table 5. Cause of death after LT and LLT for patients with CF

	LT (n = 81), %	LLT (n = 4), %	p-Value
Pulmonary	15 (22.7)	0	0.31
Hemorrhage	12 (18.2)	1 (25%)	0.81
Malignancy	11 (16.7)	1 (25%)	0.74
Renal failure	9 (13.6)	0	0.44
Graft loss	7 (10.6)	0	0.49
Stroke	5 (7.6)	0	0.56
PTLD	2 (3.0)	0	0.72
Multiple organ systems	1 (1.5)	0	0.80
Infection	0	1 (25%)	<0.01
Unknown	19 (23.5)	1 (25%)	n/a

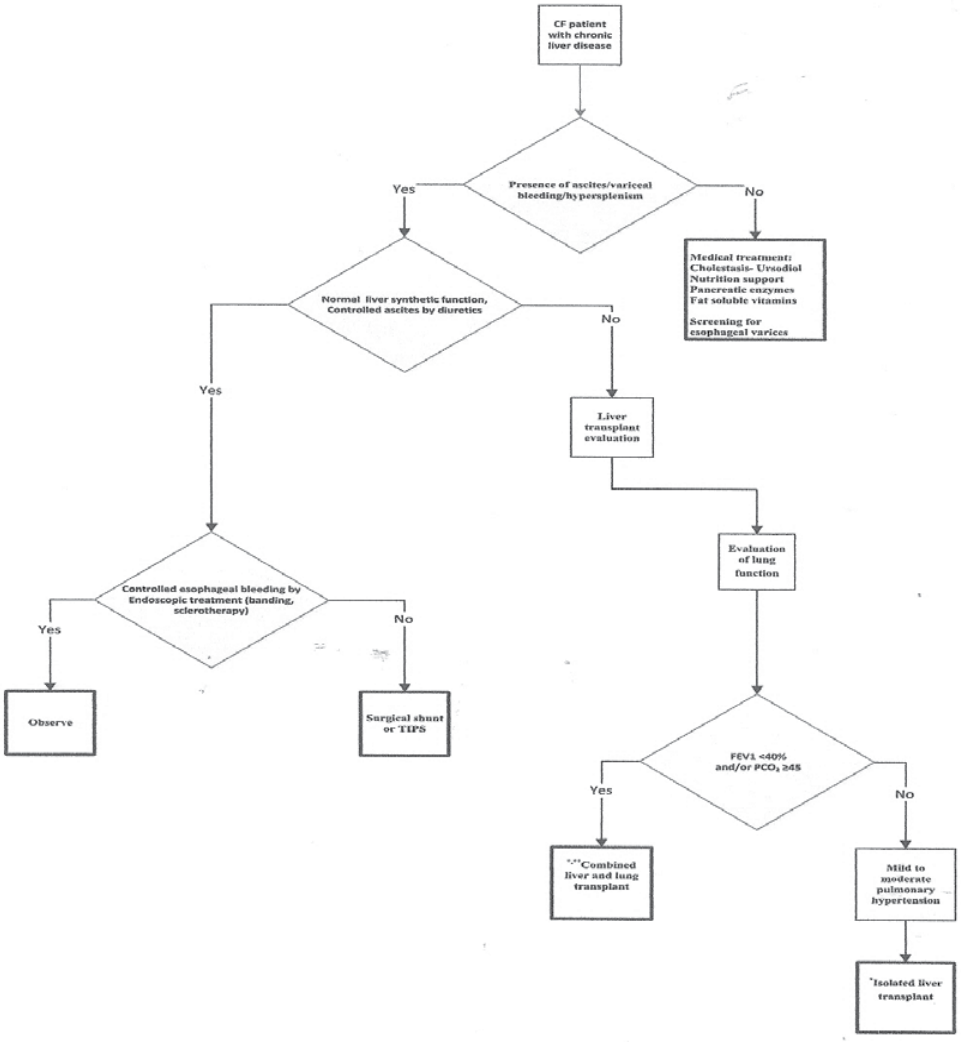


Table 6. Cause of death after LT for patients with CF, children vs. adults

	Children (n = 58)	Adults (n = 23)	p-Value
Pulmonary	13 (22.4)	2 (8.7)	0.46
Renal failure	8 (13.8)	1 (4.3)	0.46
Hemorrhage	6 (10.3)	6 (26.1)	0.01
Malignancy	6 (10.3)	5 (21.7)	0.04
Graft loss	6 (10.3)	1 (4.3)	0.66
Stroke	5 (8.6)	0	0.25
PTLD	1 (1.7)	1 (4.3)	0.31
Multiple organ systems	1 (1.7)	0	0.61
Infection	1 (1.7)	0	0.59
Cardiac	1 (1.7)	4 (17.4)	<0.01
Unknown	10 (17.2)	3 (13.0)	n/a

American Journal of Transplantation 2008; 8: 162–169
Blackwell Munksgaard

doi: 10.1111/j.1600-6143.2007.02028.x

Cystic Fibrosis Liver Disease: To Transplant or Not to Transplant?

K.L. Nash[a,*], J.D. Collier[a], J. French[b], D. McKeon[b], A.E.S. Gimson[a], N.V. Jamieson[a], J. Wallwork[b], D. Bilton[b] and G.J.M. Alexander[a]

Received 29 May 2007, revised 09 September 2007 and accepted for publication 18 September 2007

- The outcome for combined heart/lung/liver grafting in adult people with CF was poor, whereas liver transplantation alone had acceptable waiting times and good survival outcome.
- High incidence of renal impairment in this group, and in contrast to previous studies, largely in pediatric patients, respiratory function declined dramatically.

A combined liver – pancreas en-bloc transplant in a patient with cystic fibrosis.

Young A, Giles C, Mervyn T et al Transplantation 2005;5:605-607.

Method of en-bloc liver – pancreas transplant is the most efficient way to carry out this procedure. Combining liver and pancreas transplant has several advantages in patients with end-stage liver disease and IDDM.

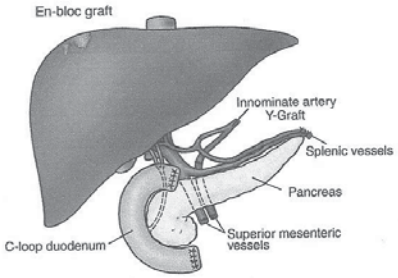


FIGURE 1. En-bloc graft.

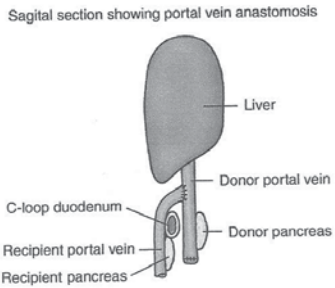


FIGURE 2. Sagittal section showing portal vein anastomosis.

Benefit of the en bloc technique

- Simpler operation with fewer anastomoses
- Physiologic insulin release into the portal circulation
- Decrease the risk of venous torsion
- Immunologic benefit of the liver acting as a sink for circulating antigen and inducing tolerance to pancreatic graft
- Simultaneous liver-pancreas transplantation restores exocrine and endocrine pancreatic function in patients with CFLD and enables improved nutritional outcomes concurrent with the potential for discontinuation of insulin and pancreatic enzyme supplementation therapies.
- Diabetes has been reprted to exert a negative effect on the already decreased pulmonary function, observed in CF patients. FEV1 in CF patients with diabetes is markedly reduced in all age groups compared to CF patients without diabetes.
- Simultaneous liver-pancreas transplantation is associated with an improved BMI in the postransplant course.

COMPLICATION AFTER LIVER TRANSPLANTATION:

Biliary complication

Stricture, leak, bile collection, biliary abscess
Ischemic-type biliary lesions
Infectious biliary complications/cholangitis

Vascular complication

Hepatic artery thrombosis
Portal vein thrombosis/stenosis
Hepatic vein outflow obstruction

Miscellaneous

Recipient and graft size
Bowel perforation

Patients with CF have a higher incidence of anastomotic biliary strictures, likely due to underlying disease of the bile duct.

Effects of using immunosuppresive drugs, such as :

- Infections
- Disorders of the hematopoetic system
- Abnormalities of the lipid and carbohydrate metabolism
- Nephrotoxicity

In patients with diagnosed cystic fibrosis following isolated liver transplantation, there is an increased risk of pulmonary complications (severe infections).
It seems that an FEV1<50% was associated with poor outcomes in isolated liver tranplantation, and thus patients with poor lung function should be considered for combined lung-liver transplantation.
For isolated liver transplantation, if the FEV1 is <40%, patients are listed with their MELD/PELD score plus a 10% mortality equivalent.

< 1 month	1- 6 months	>6 months
Infections with bacteria resistant to treatment MRSA, VRE, CANDIDA Catheter-related infections Aspiration Clostridium dificile Donor's infections HSV, HIV	Viral infections , CMV, EBV, HBV PNEUMOCYSTOSIS	Population endangerment Pneumonias Aspergillosis CMV, HBV, HCV

If listed for a combined liver-lung transplantation with an FEV1 <40%, the liver listing starts with a MELD of 40.

The viral factor in oncogenesis

- EBV – Burkitt lymphoma, nasopharyngeal cancer, PTLD
- HBV, HCV – hepatocellular carcinoma HCC
- HTLV 1- T-cell leukaemia
- HPV – cervical cancer, anogenital cancers, skin and bladder cancers
- HHV 8 – Kaposi's sarcoma

Prophilactics of the infections

- HSV Acyclovir, ganciclovir, valacyclovir, famciclovir
- VZV Acyclowir, VZV immunoglobulin
  CMV Ganciclovir, valacyclowir, acyclovir, CMV immunoglobulin anty CMV
- P.carini TMP-SMX
- Funghi Fluconazole, sterilization of the gastrointestinal tract
- Bacteria TMP-SMX
- T.gondii TM-SMX, pyrimethamine

Summary:

- **The etiopathogenesis of hepatic lesions in the course of cystic fibrosis is very complex and not yet fully explained.**
- **The clinical symptoms of CFLD are not characteristic and the clinical picture is often symptomless or limited.**
- **Further studies into the causes of hepatic lesions in cystic fibrosis are necessary, which will contribute to the reduction in the number of deaths, extended survival rate and improvement in patients' quality of life.**

SUPPLEMENTATION OF PANCREATIC ENZYMES FROM THE PERSPECTIVE OF THE GASTROENTEROLOGIST

WOŚ Halina, KRAKOW, POLAND

Pancreatic function

- production of pancreas juice 1200 - 3000 ml/day
- pancreatic enzymes: amylase, lipase, trypsin, chymotrypsin, elestase, kallikrein
- production of bicarbonates neutralizing acidic gastric contents
- maintenance of acid-base balance

Function of the pancreas controlled by the hormones of the digestive tract

- secretin → secretion of bicarbonates
- CCK: release gallbladder from gallbladder, secretion of pancreatic juice
- acetylcholine → motility and secretion of pancreatic juice
- digestive disorders <10% of normal secretion
- carbohydrate digestion already started in the mouth (salivary amylase) and stomach
- fat digestion mainly in the proximal part of the small intestine

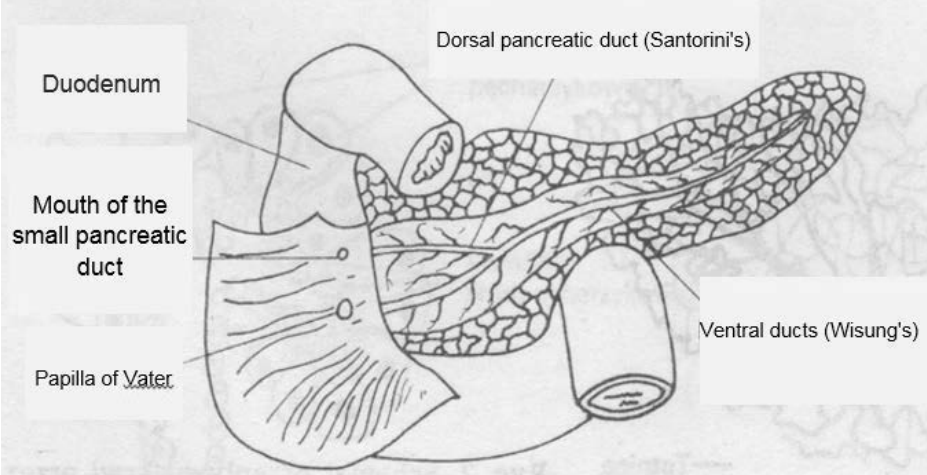
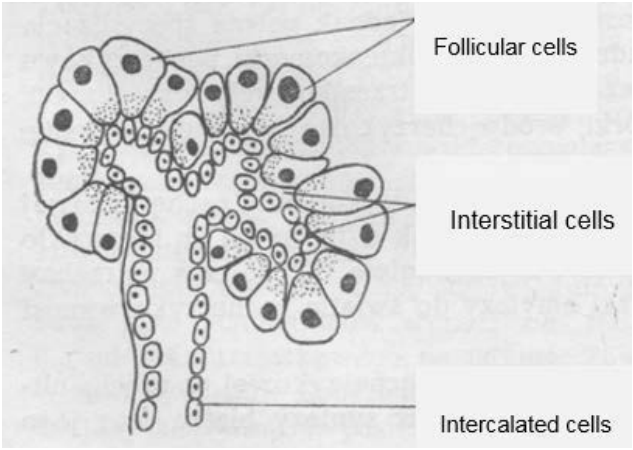


Fig. 1 Anatomy of the pancreas



ORIGINAL ARTICLE: PANCREATOLOGY

Pancreatic Enzyme Replacement Therapy and Coefficient of Fat Absorption in Children and Adolescents With Cystic Fibrosis

*Janna W. Woestenenk, †Cornelis K. van der Ent, and †Roderick H.J. Houwen

(JPGN 2015;61: 355–360)

1. SiBO (small intestine bacterial overgrowth) bacterial overgrowth (~40% of patients with CF)
   - -an increase in intestinal gas, bloating, diarrhea, steatorrhoea
   - -vitamin B12 deficiency
   - -increase in folic acid level
2. Low pH of intestinal juice – bile acid precipitation and disturbance of micellar formation
3. Sudden ejection of gastric juice duodenum pH drop denaturation of other enzymes

SUPPLEMENTATION OF PANCREATIC ENZYMES

- in all patients with exocrine pancreatic insufficiency and malnutrition
- prevents micronutrient, fat-soluble vitamins, ferritin and prealbumin deficiencies

2 000 - 4 000 IU lipase / 120ml blend/fed
1 000 IU lipase / kg b.w./meal < 4 year of life
500 IU lipase / kg b.w./ meal > 4 year of life

max dose: 10 000 IU lipase / kg b.w. / day
2 500 IU lipase / kg b.w. / meal

SUPPLEMENTATION OF PANCREATIC ENZYMES PER GRAM OF FAT INTAKE
2000 – 4000 J IU LIPASE

Pancreatic enzyme preparations approved by FDA (after April 2010)

- Creon (Abbott Laboratories, Hanover, Germany)
- Zenpep (Aptalis Pharmaceuticals, Milan, Italy)
- Pancreaze (Janssen Pharaceuticals, Uetersen, Germany)
- Ultresa (Aptalis Pharmaceuticals, Pessano, Italy)
- Viokace (Aptalis Pharmaceutocals, St. Hubert, Canada)
- Pertzye (Digestive Care, Inc, Bethlehem PA)

Berry. Nutrition in Clinical, Practice 2014

Pancreatic enzyme preparations available in Poland

Tabela C.15-2. Skład i postać farmaceutyczna dostępnych w Polsce preparatów pankreatyny

Lek	Postać	Skład			Kategoria dostępności
		lipaza (j. Ph. Eur.)	amylaza (j. Ph. Eur.)	proteaza (j. Ph. Eur.)	
Kreon 25 000	kaps. dojelitowe (minimikrosfery)	25 000	18 000	1000	Rp
Kreon 40 000	kaps. dojelitowe, twarde (minimikrosfery)	40 000	25 000	1600	Rp
Kreon Travix	kaps. dojelitowe (minimikrosfery)	10 000	8000	600	OTC
Pangrol 10 000	kaps. (minitabletki)	10 000	9000	500	OTC
Pangrol 25 000	kaps. (minitabletki)	25 000	22 500	1250	OTC
Neo-Pancreatinum Forte	kaps. dojelitowe (peletki)	10 000	8000	500	Rp

j. Ph. Eur. – jednostki Farmakopei Europejskiej, OTC – preparat bez recepty, Rp – preparat na receptę

PANCREATIC ENZYMES

The enteric capsules release the lipase in the duodenum pH >5,5
mini microspheres 1,0 - 1,2 mm
mini microspheres 1,8 – 2,0 mm

Swallow! Do not chew it! Do not crush!

(optionally mix with the acid environment)

Forms: powder, granules, tablets, microspheres, mini microspheres

ORIGINAL ARTICLES www.jpeds.com • The Journal of Pediatrics

Pancreatic Enzyme Replacement Therapy Dosing and Nutritional Outcomes in Children with Cystic Fibrosis

Mark E. Haupt, MD[1,*], Mary J. Kwasny, ScD[2], Michael S. Schechter, MD, MPH[3], and Susanna A. McColley, MD[1]

1755 IU lipase /kg b.w./meal vs 1628 IU lipase

weight BMI	50,7 vs 39,6
hight BMI	40,4 vs 31,6
b.w. deficiency	37% vs 45%
steathor	26% vs 39,5%
FEV1	90,3 vs 81,3

ELSEVIER
Journal of Cystic Fibrosis 15 (2016) 669–674
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Preliminary report of the ^{13}C-mixed triglyceride breath test to assess timing of pancreatic enzyme replacement therapy in children with cystic fibrosis

Natalie van der Haak [a,*], Julia Boase [a], Geoffrey Davidson [b], Ross Butler [b,1], Michelle Miller [c], Billingsley Kaambwa [d], Stamatiki Kritas [b,2]

[a] Department of Nutrition, Women's and Children's Hospital, North Adelaide, South Australia, Australia
[b] Department of Gastroenterology, Women's and Children's Hospital, North Adelaide, South Australia, Australia
[c] Nutrition and Dietetics, School of Health Sciences, Faculty of Medicine, Nursing and Health Sciences, Flinders University, Adelaide, South Australia, Australia
[d] Flinders Health Economics Group, School of Medicine, Flinders University, Adelaide, Australia

Received 20 October 2015; revised 23 March 2016; accepted 31 March 2016
Available online 19 April 2016

Evaluation of lipase activity 10' before and after meal

- decreased in case of gastric emptying disorders
- administration 10' after a meal has no effect on its performance
- better results with supply during or after a meal

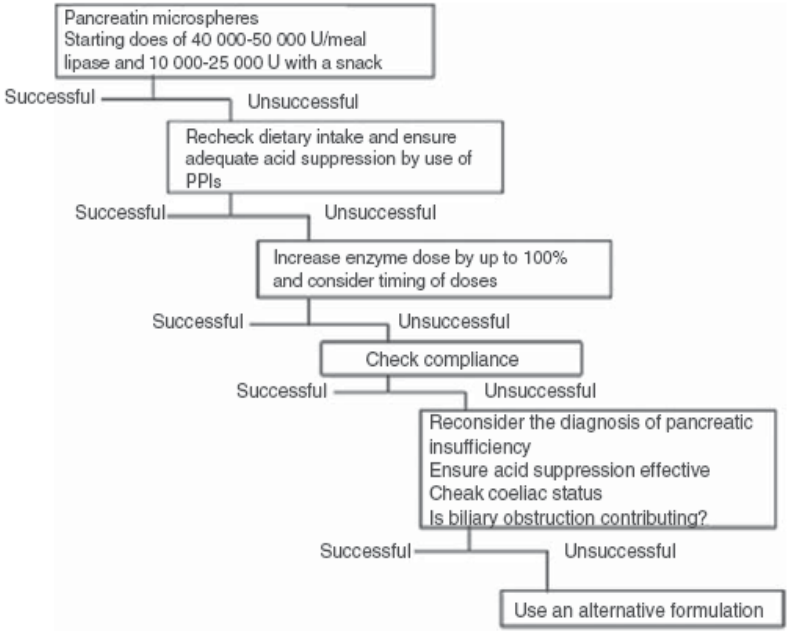
Enteric – coated enzymes a PPI/H2 bloke

- secretion of bicarbonate is not proportional to the abnormal secretion of enzymes by the pancreas
- no response to pancreatic enzymes - consider using Ppi
- motility disorders, delayed gastric emptying, accelerated intestinal transit

Sander-Struckmeier. Pancreas 2013

Evaluation of PERT's effectiveness

- improvement of clinical parameters (disappearance of bloating, abdominal pain)
- systematic weight gain
- disappearance of fatty diarrhoea



Lack of efficacy of PERT

- inadequate dosage
- storage of enzymes at too high temperatures
- failure to follow the recommendations
- low pH in the duodenum – inactivation of lipase pH <4 blockage of enzyme re lease from the shell
- bacterial overgrowth in the small intestinenieodpowiednia dieta rich in fiber: absorption of pancreatic enzymes delayed absorption rich in Ca and Mg: increased precipitation of bile acids consider MCT fats: absorption in the small intestine without lipase, colipase and bile

Side effects of PERT use

- Nausea
- Bloating
- Feeling of fullness
- intestinal cramps
- too high doses combined with fibrosing colonopathy

OPTIMAL DOSE IS NOT KNOWN SPECIFICALLY FOR EVERYONE

ELSEVIER

Journal of Cystic Fibrosis 12 (2013) 784 – 785

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Short Communication

Maximal daily dose of pancreatic enzyme replacement therapy in infants with cystic fibrosis: A reconsideration

Drucy Borowitz [a,*], Daniel Gelfond [a], Karen Maguiness [b], James E. Heubi [c], Bonnie Ramsey [d]

[a] State University of New York at Buffalo School of Medicine and Biomedical Sciences, Department of Pediatrics, Women and Children's Hospital of Buffalo, Buffalo, NY, United States
[b] Riley Hospital for Children at Indiana University Health, Indianapolis, IN, United States
[c] Cincinnati Children's Medical Center and University of Cincinnati Department of Pediatrics, Cincinnati, OH, United States
[d] University of Washington School of Medicine, Department of Pediatrics, Seattle, WA, United States

Received 5 April 2013; accepted 24 May 2013
Available online 26 June 2013

Lack of knowledge of optimum introduction time of PERT and the appropriate dosage for the different degrees of pancreatic insufficiency, especially in infants

Another form of enzymes

- Insoluble form in the intestine

Viokace Aptalis Pharmaceuticals, St. Hubert Canada

- Necessity to use together with IPP - enzymes can be deactivated in the stomach (not available in Poland)

Berry. Nutrition Clinical in Practice 2014

Nutritional treatment

- Dietary intervention to increase the amount of calories, including oral dietary supplemen tation
- Enteral nutrition through a nasogastric tube or PEG
- Parenteral nutrition
- NIGHT ENTERAL NUTRITION COMPLETES DAILY CALORIE INTAKE AND DOES NOT RE PLACE NORMAL MEALS (~ 30%)

Enzyme therapy during enteral feeding

- calculate the enzyme dose per 1 gram of fat
- orally 3/4 of the dose at the beginning of the supply and 1/4 before the end
- Enzymes - enteric form – microspheres dissolve in natrium bicarbonatu or 1/4-1/2 a teaspoon of soda + 30ml, H20, dissolved enzymes afte 15-30` add to the feeding bag
- Enzymes - insoluble form in the intestine - mash and add to the nutritional bag (note not to inhale the powder and save your eyes)
- calculate the enzyme dose per 1 gram of fat
- orally 3/4 of the dose at the beginning of the supply and 1/4 before the end
- Enzymes in the enteric form – microspheres dissolve in natrium bicarbonatu or 1/4-1/2 a teaspoon of soda + 30ml, H20, dissolved enzymes afte 15-30` add to the feeding bag
- Enzymes in insoluble in the intestines form mash and add to the nutritional bag (note not to inhale the powder and save your eyes)

Tab. Causes of failure to follow the recommendations in cystic fibrosis Conway et al. Thorax 1996

Reason for non-compliance with therapy	% reasons
I forget about it	34.5
Too much effort / takes too much time	31.4
I do not think it has any effect	12.9
Instead I perform physical exercise (this only applies to physiotherapy)	7.4
It is embarrassing (pancreatic enzymes and physiotherapy)	4.4
I do not feel good after that	4.4
It has a bad taste (antibiotics in nebulisation and inhaled corticosteroids)	1.2
I am not convinced that I should take it	0.7
Other reasons	4.4
Total	100

Cystisorb™

FOR THE DIETARY MANAGEMENT
OF MALABSORPTION OF VITAMINS A D E K IN PATIENTS
WITH **CYSTIC FIBROSIS AND CHOLESTASIS**

- Unique formula of vitamins and microelements
- Formula fortified with a high dose of vitamin K2 MK-7
- Source of vitamins A D E K
- MCT - based fill for better absorption
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Cystisorb is a dietary food for special medical purposes dedicated to the dietary management in cases of malabsorption of vitamins A D E K in patients with **cystic fibrosis** and **cholestasis.**

Cystisorb is a dedicated solution for individuals with cystic fibrosis and cholestasis, developed based on the latest scientific evidence. Cystisorb supports supplementation of specific deficiencies of vitamins and trace elements, in particular fat-soluble vitamins: A D E K. The formulation was created in collaboration with recognised experts in the field of gastroenterology.

Cystisorb contains a unique composition of vitamins and minerals, including 200 mcg of vitamin K in both naturally occurring forms: 100 mcg of phylloquinone (vitamin K1) and 100 mcg of menaquinone (vitamin K2 MK-7). Cystisorb is the only solution for individuals with cystic fibrosis on the market containing vitamin K2.

Fat-soluble vitamins A D E K per 1 Cystisorb™ capsule:			
Vitamin A: 5000 IU (1515,1 µg), of which: beta-carotene: 4000 IU (1212,1µg) retinyl palmitate: 1000 IU (303 µg)	**Vitamin D3: 3000 IU (75 µg)**	**Vitamin E: 150 IU (100,7 mg)**	**Vitamin K: 200 µg,** of which: vitamin K1: 100 µg vitamin K2 MK-7: 100 µg

Nutrition Information	Per 100 g	Per 1 Capsule
Vitamin A	196766,2 µg	1515,1 µg
Vitamin D	9740,3 µg	75 µg
Vitamin E	13077,9 mg	100,7 mg
Vitamin K	25974,0 µg	200 µg
Vitamin C	3116,9 mg	24 mg
Thiamin	42,9 mg	0,33 mg
Riboflavin	54,5 mg	0,42 mg
Niacin	623,4 mg	4,8 mg
Vitamin B6	54,5 mg	0,42 mg
Folic Acid	7792,2 µg	60 µg
Vitamin B12	97,4 µg	0,75 µg
Biotin	1948,1 µg	15 µg
Pantothenic Acid	233,8 mg	1,8 mg
Zinc	649,4 mg	5 mg
Selenium	2922,1 µg	22,5 µg
Coenzym Q10	389,6 mg	3 mg

www.**cystisorb.com**

Producer: Norsa Pharma Sp. z o.o., ul. Czerwone Maki 84, 30- 392 Kraków

THE ANTI-INFLAMMATORY TREATMENT OF RESPIRATORY TRACT IN CHILDREN WITH CF INCLUDING ANTIBIOTIC THERAPY

Božena KORDYS-DARMOLIŃSKA
Upper Silesian Children's Health Center in KATOWICE, POLAND

Anti-inflammatory therapy - preventing the progression of pulmonary disease

- This is the primary goals of CF treatment
- The average life expectancy of patients with CF, in the last four decades, has significantly increased - The medi an survival reached about 40 years in 2011
- Still, the majority of patients die from respiratory failure

Prevention of progression of pulmonary disease

- Cystic fibrosis mutations lead to impairment of muinfe cociliary clearance which results in occlusion by mucus plugs and secondary pathogenic infections - staphylococ cus aureus and pseudomonas aeruginosa type.
- Chronic infections and inflammation with massive neutrophil infiltration are intensified by exacerbation
- after exacerbation, lung functions do not return to baseline values
- Meticulous, daily monitoring and management of lung disease
- Fast and aggressive treatment of exacerbations is the key to maintaining lung functions
- First untreated P.A infection leads to chronic infection with impaired lung function, poorer nutrition, increased pulmonary exacerbation and higher mortality
- eradication introduced not later than 4 weeks after the positive result of culture

Available options

- Tobramycin inhalation solution (TIS) for 28 days
  and
- lasting up to 3 months, combination therapy with colistin with nebulized ciprofloxacin
- Chronic P.A infection indication for long-term inhaled antibiotics therapies (for life)
- Colistine 2x2mln / day widely used in Europe

It is also currently available in the form of a dry powder

Colistine

- Inhalation form - dry powder, capsules
- trade name COLOBREATHE
- dose of 1 662 500 IU = 125 mg 2x / day for 28 days with a manual inhaler of the Turbos pin type
- effect comparable to a solution
- easy to use

- Inhaled Tobramycin 2 x 300 mg for 28 days with the interval of 28 days without treatment, in patients > 6 years of age, according to the US guidelines
- TOBI Podhaler TM (tobramycin) Powder has similar efficacy
- Alternative treatment with aztreonam lysine (European and American guidelines)

Tobramycin

- Inhalation solution - company name TOBI or BRAMITOB
- dose of 300 mg / 5 ml or 4 ml administered 2x / day for 28 days with a 28 day interval
- inhalation form - dry powder - company name TIP
- dose of 112 mg 2x / day for 28 days using a podhaler
- may be oto-, nephrotoxic, induce bronchospasm

Aztreomon

- Company name CAYSTON or AZLI
- 75 mg administered by nebulization 2x / day for 28 days with 28 day interval
- Tobramycin may be used in the interval
- treatment of P.A. infections
- studies in chronic infections of Burkholderia cepacia
- Chronic infection with other bacteria than P.A- Antibiotic therapy continuous maintenance is not indicated
- The controversial use of flucloxacillin in early life to prevent Staphylococcus aureus infection
- Ceftaroline new cephalosporin acting on MRSA
- Progression with alternating period of stabilization and pulmonary exacerbations (PEX)
- There is no clear definition of PEX
- It requires a multidisciplinary approach
- Intensive antibiotic therapy with the participation, in the selection, of a pharmacist, a microbiologist and a specialist in the treatment of infectious diseases
- Selection of method of airway clearance with optimization of inhalation therapy (cooperation with physiotherapist)
- Increasing the supply of calories due to higher metabolic demands (working with a dietician)
- Control of enzyme and vitamin supplementation
- psychological support

PREVENTION OF PROGRESSION OF PULMONARY DISEASE- ANTIBIOTIC THERAPY

- Hospital care is the optimal standard of care for most patients requiring intravenous antibiotics
- In individual cases it is possible to use intravenous antibiotic therapy in the patient's home
- Dosage should be adjusted according to the guidelines of the disease, taking into account the required higher dose of antibiotic
- recommended combination therapy using two or more antibiotics
- routine treatment for 14 days, in some cases longer - 3-4 weeks

- Use of inhaled antibiotic therapy in the standard treatment of patients with CF
- effective in reducing pulmonary exacerbations in patients with CF
- improves lung function
- reduces respiratory tract symptoms
- Long-term inhalant antibiotic therapy given with one drug or different kinds of antibiotics administered alternately
- high local concentration of the antibiotic
- outweighs the risk of developing resistance to antimicrobial drugs

Amikacin
- Liposome inhalation provides deep mucus and bacterial biofilm penetration
- company name ARIKACE
- dose of 560 mg / day via a PARI LC STAR or e-FLOW inhaler for 28 days
- attempts to treat multidrug-resistant pathogens - Mycobacterium abscessus type and other Nontuberculous mycobacteriosis
- consider Prevotella infection or other anaerobes

Levofloxacin
- Company name AEROQIN
- dose 240 mg administered by nebulization 2x / day for 28 days with 28 day interval
- Tobramycin may be given during the interval
- treatment of P.A. infections
- may cause a taste disorder

PREVENTION OF PROGRESSION OF PULMONARY DISEASE - ANTIBIOTIC THERAPY

Macrolides
- Distort the production of alginates - conducive to antibacterial activity of other antibiotics and phagocytes
- <PEX frequency, improve bronchial obstruction
- patients after 6 years of age (25-40 kg) - 3 times per week or every other day with 250 mg
- patients after 6 years of age> 40 kg - 500 mg or 250 mg daily
- Dosage in children <6 years - not recommended in children <5 kg body weight, average dose 10 mg / kg 3 times a week
- recommended for chronic treatment

Mogayzel PJ Cystic fibrosis pulmonary guidelines AmJ Resir.2013

- possibility of developing resistance to other bacterial strains
- Anti-inflammatory and anti-adhesive
- do not work very well on P. auginosa but are effectively antibacterial to biofilm forming microorganisms as occurs in chronic P. aeruginosa infection
- chronic administration improves lung function

Prevention of progression of pulmonary disease- ABPA

- Recurrent allergic bronchopulmonary aspergillosis - Aspergillus fumigatus and other types of fungi often in sputum of patients with CF
- always be considered in patients with clinical deterioration unresponsive to antibiotics

UK Cystic Fibrosis Trust 2009

- Recurrent allergic bronchopulmonary aspergillosis - diagnostic tests: allergy skin test, eosinophilia
- Determination of serum total IgE (> 1000 IU), sIgE for Aspergillus, presence of antibodies against Aspergillus
- in the chest x-ray infiltrations of recurring character and in HRCT central bronchiectasis with finger-in-glove shadow.
- Treatment: length of therapy and dose of the drug individually selected for the patient
- Prednisone 0.5-1 mg / kg b.w. for 2 weeks then 0.5 mg / kg b.w. every 2 days for the next 2 weeks
- dose reduction and discontinuation of treatment in 2-3 months
- itraconazole and voriconazole for 3-6 months

Prevention of progression of pulmonary disease – Mucokinetics

- Dornaza alpha - the only mucolytic preparation with proven efficacy
- improves lung function and <number of exacerbations irrespective of severity of disease
- slows progression of the disease
- The effectiveness of other mucolytic drugs including N-acetylcysteine in CF has not been demonstrated

KonstanMW,Wagener Ped.Pulmonol 2011

Prevention of progression of pulmonary disease – Moisturizers

- Increased amount of fluid on the surface of dehydrated airways can be achieved by wetting osmotic agents:
- Hypertonic NACI (7%) - <frequency of exacerbation and slightly improve pulmonary function in moderate to severe CF

WarkP,McDonaldVM Cochrane Databa se syst Rev.2009.

- Mannitol, introduced recently for treatment, improves lung function
- available in the form of powder for inhalation, which shortens the duration of treatment
- NaCl and Mannitol are irritating to the respiratory tract and require initial assessment of tolerance and premedication with bronchodilator

Aitken ML,Bellon Am J Respir Crit CareMe2012

Prevention of progression of pulmonary disease – physiotherapy

- is an indispensable part of CF treatment
- positive expiratory pressure (PEP) has the advantage over high frequency chest wall oscillation (HFCWO)
- airways clearance techniques should be selected individually

Prevention of progression of pulmonary disease – CFTR modulators

- Drug therapy directed towards the CFTR is intended to increase increased expression of proteins on the surface of cells their activities
- Ivacaftor - CFTR amplifier, in patients with G551D gating mutation (<5% of patients world wide), concentration of chlorides in sweat, improves clinical indicators
- Orkambi - in patients> 12 years of age with del508F mutation (250 mg Lumacaftor / 125 mg Ivacaftor)

BREAKING THE NEWS OF GENETIC DISORDER - THE EXPERIENCE OF POLISH PARENTS AND CARERS

Maria LIBURA, Institute for Interdisciplinary Studies, Lazarski University, WARSAW, POLAND
Aldona JANKOWSKA, Department of Paediatrics, Haematology and Onocology, Nicolaus Copernicus University in Toruń Collegium Medicum in BYDGOSZCZ POLAND

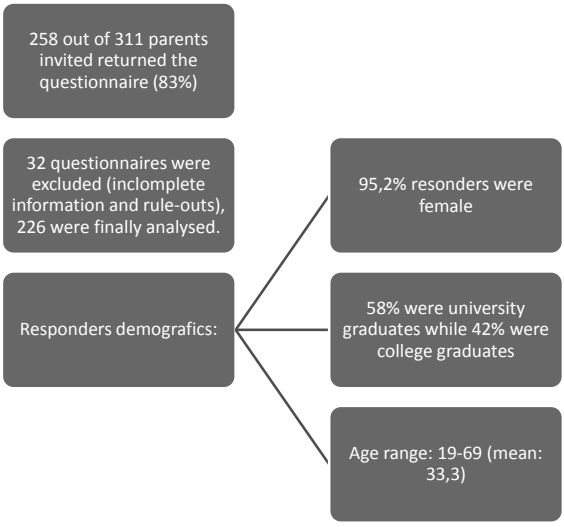
Background

- The news of a genetic deasese diagnosis is a life – changing experience for parents.
- The way the news is conveyed may have a lasting impact on parental attidute and coping strategies.
- There is limited data on the practice and the experience of parents/carers of patients with such disorders in Poland.
- The purpose of this study was to investigate the experience of Polish parents and carers in order to propose a set of recommendations on good practice in this area.

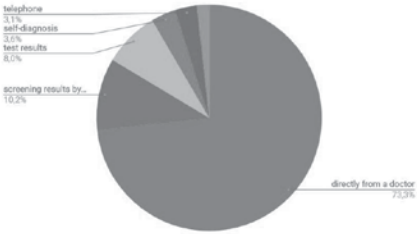
Method

1. Focus group were run to identify the main issues related to parent experiences of genetic condition diagnosis delivery.
2. An anonymous questionnaire, prepared on the basis of Focus group results and literature review, was distributed among parents via genetic disease patient associations.
3. Quantitative data were analyzed using descriptive statistics. Qualitative data were analyzed using discourse analysis tools.

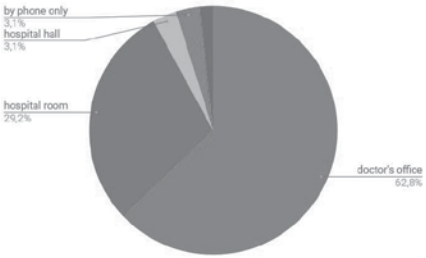
Responders



How did you learn about your child's genetic condition?

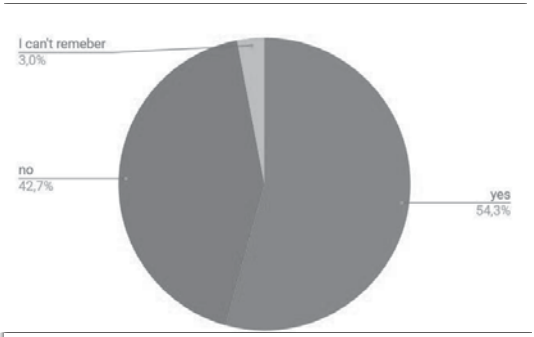


Diagnosis discussion setting



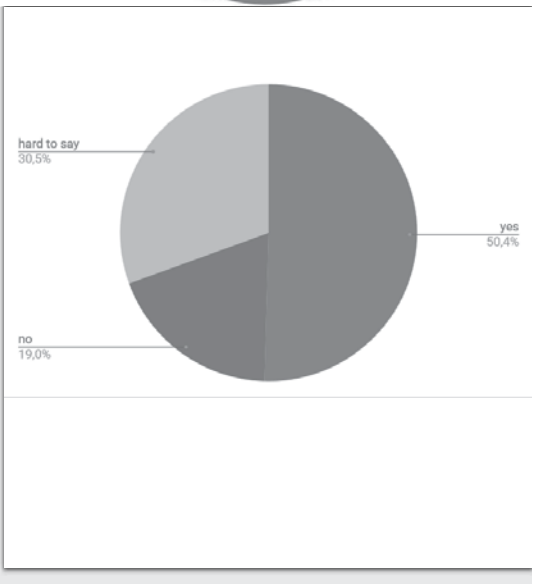
Were both parents invited to participate?

88% of respondents declared that they preferred both parents to be present at the time of diagnosis delivery.

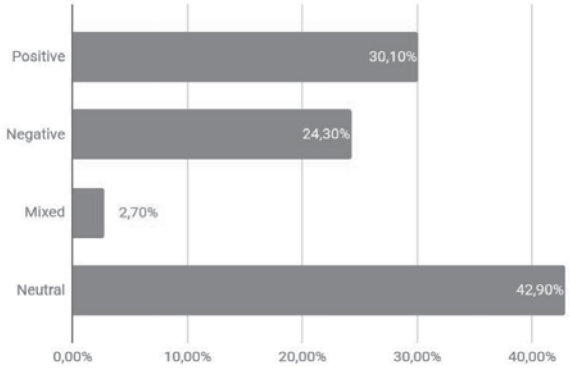


Was the diagnosis explained in a clear way?

- 70% declared patient associations and ther parents proved to be the most useful sources of information on their child's condition in the months following diagnosis
- Only 5 (!) responders regarded doctors or other medical professionals as the most useful source of information



Parents' experience



Examples of positive interaction

- The tone was warm and the lanuage was easy to understand.
- The message was: the syndrome requires some extra effort, but you can live with it.
- The doctor was calm, had an information package ready for us, and encouraged us to ask questions.
- I knew what to do next in terms of care.
- The doctor said our baby was cute.
- „We are here for you and we will suport you", the doctor said.

Examples of negative interaction

- „Bingo! We hit the bullseye" – the doctor expressed satisfaction with her diagnostic skills.
- The doctor asked straight away if she could take a picture of our baby that she would use in her future presentatons at conferences.
- The doctor warned at the outset that she had no more than 5 minutes for us.
- „It's bad luck."
- The doctor recited a litany of symptones in a disinterested tone.
- The doctor suggested placing our baby in a permanent care setting.
- „Think twice before you share this diagnosis with anyone"

Diagnosis is a point of departure

- 65% of respondents were not satisfied with the information they received atthe time of diagnosis.
- 40% declared no information on „what to do next" was provided.

Conclusions

- Assuring adequate setting and time for breaking bad news is essential.
- Hospital setting proves more challenging for parents.
- Focusing solely on generic reference to symptoms characteristic for a given condition dehumanizes the child as it becomes an instance of a genetic condition
- Diagnosis delivery is a point of departure for parents; they expect guidance on next steps in medical care.
- Provision of practical „what to do next" information is as important to parents as is emphathetic attitude.

MENTOR PROJECT - SUMMARY OF THE THREE YEARS OF EXPERIENCE

MARSZAŁEK Przemysław[1], BORAWSKA-KOWALCZYK U.[2,3], SANDS Dorota[2,3]
[1]'Matio' Polish Cystic Fibrosis Foundation, KRAKÓW, POLAND
[2]Institute of Mother and Child, Cystic Fibrosis Department, WARSZAWA, POLAND
[3]Dziekanow Lesny Hospital, Cystic Fibrosis Center, DZIEKANOW LESNY, POLAND

The diagnosis of cystic fibrosis (CF) in a child is a traumatic time for all parents. All hopes and plans for the future are shattered in an instant. What follows is, time-consuming treatment regime, immeasurable responsibility, emotional distress and changes in family structure. All of this could be a cause of feeling overwhelmed and disoriented. At this time social support is especially needed.

Objectives:
Help and support for new "CF parents" no longer then 24h after diagnosis.

Methods:

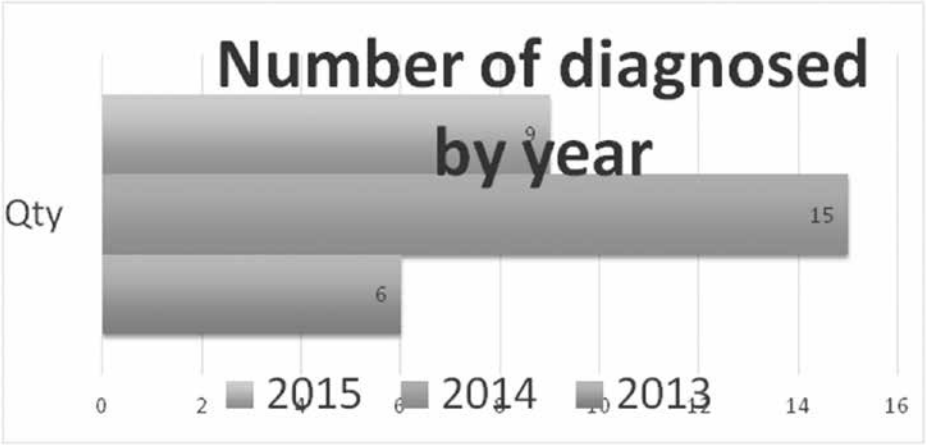
A. The project was the initiative of "*Matio*" Polish Cystic Fibrosis Foundation in collaboration with the CF Center in the Institute of Mother and Child in Warsaw. The idea was to support parents of newly diagnosed children with CF by another parent of child suffering from this illness.

B. The Mentor is a person who has experienced similar traumatic time during the diagnosis of CF. He/she meets the family as soon as possible after the diagnosis in CF Center.

C. Two hospitals took part in the project:
1. Institute of Mother and Child in Warsaw
2. The Independent Public Clinical Hospital no. 6 of the Medical University of Sile sia in Katowice

Results:

- The **2 Mentors** took part in the project. They had met 30 newly diagnosed families during the period of **36 months**.
- The Mentor provides various kind of assistance:
  Information support - educational materials "practical tips" developed by the Foundation (e.g. where to buy the cheapest drugs, how to sterilize equipment, how to prepare an flat).
  Conversation - to share own experiences.
- Maintaining contact after diagnosis: Periodic telephone contact.



Conclusion:

- Parents after the diagnosis of cystic fibrosis in a child willingly agreed to the proposal of a meeting with the Mentor.
- Relations between mentors and parents are strong and continues to this day.
- Parents recall obtained assistance as very necessary, important and irreplaceable
- Project “Mentor” has been extended to the next CF Centre in Krakow.

MATIO
Polish Cystic Fibrosis Foundation

Instytut Matki i Dziecka

PHYSIOTHERAPY IN CYSTIC FIBROSIS

Natalia JENERALSKA, Centrum Leczenia Mukowiscydozy, Szpital w Dziekanowie Leśnym
WARSZAVA, POLAND

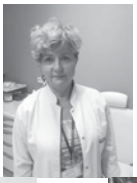
„The CF Physiotherapist should be available for regular contact and assessment of the patient for treatment, lung function testing, physical surveillance and therapy evaluation. The frequency of this will vary according to the patient's age and clinical status but as a minimum should happen at every routine outpatient clinic and daily during each hospitalization (including when patients are admitted under the care of other specialists and to intensive care). A more extensive assessment should take place annually"

European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre, Journal of Cystic Fibrosis 13 (2014) S3–S22

CENTRUM LECZENIA MUKOWISCYDOZY
DZIEKANÓW LEŚNY

There are 4 physiotherapists in The Cystic Fibrosis Center team:

- One in the Cystic Fibrosis Clinic



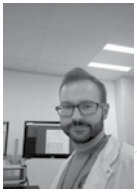
Ela

- Two in a hospital ward

Ola

Natalia

- One in the exercise test lab/hospital ward



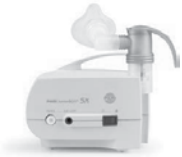
Michał

- There are about **400 CF** patients under our care
- About 4 weeks old (screening newborns) - to the age of 18
- A comprehensive physiotherapy is performed immediately after diagnosis.
- With the patient's age and progress of the disease modifications are made.

BABIES

Inhalations

- Inhalation is performed using a nebuliser with a mask
- Proper selection of an inhaler, a nebulizer and a mask
- Proper sterilization and storage of an inhalation equipment



Airway clearance

Postural drainage in 4 drainage positions. About 3 minutes on each side with chest clapping

- At about 3 months of age we start using PEP (Positive Expiratory Pressure) with a mask, belts for bronchial drainage and a rehabilitation ball
- At about 5 - 6 months of age we implement Assisted Autogenic Drainage in a semi-recessive position or seating on parent knees (while parent is sitting on rehabilitation ball, swinging and slighly jumping) with PEP and drainage belts

General development exercises

- stimulating psychomotor development exercise (NDT- Bobath)
- Exercises that improve chest movement.

SMALL CHILDREN (1 - 3 YEARS OLD)

Inhalations

- Replacement of the mask on the mouthpiece and nose clip during inhalation – max. in 3 years of age

Airway clearance

- Assisted Autogenic Drainage in different positions
- PEP with mouthpiece
- Respiratory exercises (soap bubbles, birthday trumpet, small balls, candles e.t.c.

Physical activity

- General development exercises
- Jumping, trampoline, biking

PRESCHOOL CHILDREN (3 - 6 YEARS OLD)

Inhalations

- Mandatory passage from the mouthpiece to the mouthpiece and nose clip
- Proper selection of an inhaler and a compressor
- Children learning a self-made inhalation





Airway clearance

- Assisted Autogenic Drainage in different positions
- PEP
- Learning the proper exercise of inhalation and exhalation, controlled breathing and intense exhalation
- Introducing elements of an Active Breathing Cycle
- Progressive implementation of o - PEP (Oscillating Positive Expiratory) equipment





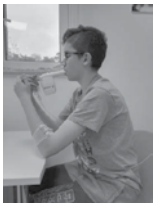
Physical activity

- Corrective gymnastics
- General development exercises
- Dancing classes
- Biking
- Trampoline jumping
- Scooter e.t.c.

SCHOOL CHILDREN (7 - 13 YEARS OLD)

Inhalations

- Self-made inhalation
- Learning to combine inhalation with drainage using:


O PEP


PEP

Airway clearance

- o - PEP

- PEP

- Techniques of an Active Cycle of Breathing
- Learning Autogenous Drainage (inhaling and exhaling properly)
- Belts for bronchial drainage during the entire drainage cycle

Physical activity as a form of drainage !!!

- Patients at school age often train different sports
- We try to put them in a daily drainage pattern.

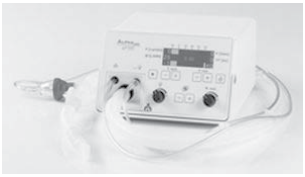
TEENAGERS (14 - 18 YEARS OLD)

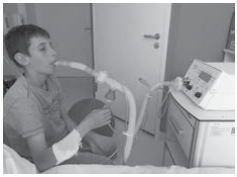
Inhalations

- At this age, we begin to require our patients to be fully familiar with the way nebulization is performer
- The equipment on which they perform inhalation
- Types of nebulizers
- How to sterilize equipment and how to perform it

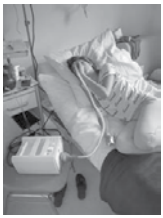
Airway clearance

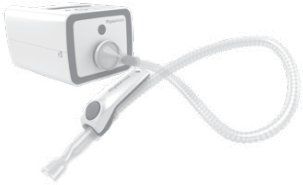
- PEP
- O PEP
- Techniques of an Active Cycle of Breathing
- Autogenic Drainage
- NonInvasive Mechanical Ventilation
- Alpha 300 - device for intermittent positive pressure breathing (IPPB)

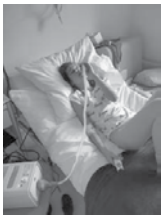




- Simeox - Vibrating pneumatic signal generator. Generates negative pressure (underpressures). Thickens and allows the secretion to remove from the airways.







Physical activity as a form of drainage!

- Football
- Handball
- Ballet
- Artistic gymnastics
- Swimming
- Horse riding
- Biking
- Running
- Aerobics
- And else

SUMMARY

- **Propper nebulization**
- **Various forms of Airway clearance**
- **Implementation in drainage a variety of technics and mechanical equipment that helps to move secretions from the airways**
- **Physical activity**

HOCUS POCUS MUCUS
How to relieve patients from sticky mucus

Florence DANET, Muriel HAMON, PHYSIOASSIST, FRANCE
Hughes GAUCHEZ, Respiratory Physiotherapist, FRANCE



The clearance of secretions from the lungs of patients with cystic fibrosis is an important component in the fight to preserve their lung function.
Different airway clearance techniques (ACT) currently exist in the market but none really stood out as being superior to another.
Patient preference is a key element and is driven by perceived efficacy and comfort.

What is the Simeox technology?
Simeox assists the bronchial drainage for patients suffering from chronic pulmonary disorders. By a direct action on the rheology of the mucus, while the patient is passively expiring, Simeox liquefies and transports the mucus from the distal part of the lungs to the central airways.
Patient's energy is preserved as the use of the device is done in total relaxation.

Fundamental research on bronchial mucus rheology done in partnership with *CNRS and Inserm* have shown:

- Bronchial mucus is a thixotropic material:
  - It can liquefy in less than 2 sec.
  - When stimulation stops, it gets back to its initial shape in less than 2 sec.

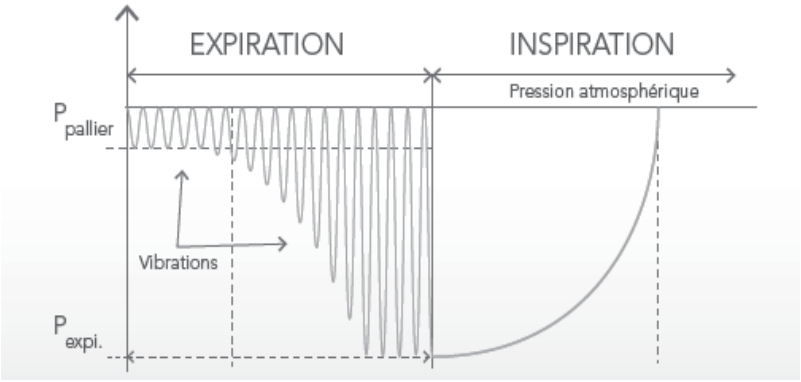
- Liquification and drainage quality are dependent on:
  - The **quality** of the signal
  - The **frequency** of the signal
  - The **power** of the intrapulmonary depression
  - The **duration** of the stimulation

Simeox generates successive and rapid depressions while in between going back at atmospheric pressure in order to prevent physiological airway collapse.
It is fundamental that the patient is trained on how to use the device by a physiotherapist.

The use of the device is based on the Autogenic Drainage technique:

- **Quality of the inspiration (no air = no action)**
- **Passive expiration (sigh)**
- **Volume management (controlled tidal volume breathing to reach distal part of the lungs)**
- **No cough to avoid bronchi collapsus**

A touchscreen interface provides real-time data to give feedback to the patient related to its use of the Simeox device.



Since the 70's, the clinical approach regarding the airway clearance techniques has evolved along with a better understanding of the lung physiology :

- Ketchup bottle
- Postural drainage
- Clapping
- ....

In 1994, the French consensus conference on ACTs recommends the use of expiratory flow modulation breathing techniques such as ACBT, AFE, ELPr, ELTGOL, Autogenic drainage.

Simeox Clinical Experience and Feedback

Whatever the technique utilized, a pre-requisite for a successful airway clearance session is the preparation of the mucus.

NO MUCUS PREPARATION = FAILED AIRWAY CLEARANCE SESSION

MUCUS PREPARATION

Hypertonic Saline

Hydration

Salbutamol

Pulmozyme

Physical Activity

MUCUS DRAINAGE

AUTOGENIC DRAINAGE
No contra indications, no dyspnea increase, no fatigability increase, no worsening of the bronchial instability

Correct position of the patient

Deep and homogenized inspiration targeting the impacted lung territories to generate alveolar pressure

Generate homogenous high speed expiratory flow to move the secretions with no collapse of the bronchi

No cough until the secretions are in the central airways and need to be expectorated

No effort from the patient, the patient is relaxed

Main advantages/outcomes of the Simeox:

- **Remove secretions even in difficult patients**
- **Patient does not provide any active physical effort, patient's energy is preserved**
- **Significant reduction of the thoracic distension**
- **Patient is relaxed and feels the benefit**

Simeox Demonstration

Simeox sessions done by Hughes Gauchez, physiotherapist in Lille (France), with one of his cystic fibrosis patients

Simeox session done by Sophie Jacques, physiotherapist in Rennes (France), with one of her cystic fibrosis patients

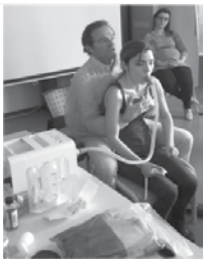
Simeox Training

Key for success: Patients, physicians, physiotherapists

- Understand
- Know how to manage
- Adapt
- Improve autonomy

We offer…

- **A training program**
- **Coaching**
- **Follow up**



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Physiotherapist,
President of the French association « mucoviscidose et kinésithérapie »

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Physiotherapist,
Pediatric CRCM « centre de référence et de compétences pour la mucoviscidose » Necker Hospital Paris

Muriel Hamon
Physiotherapist
NIV and Airway Clearance Specialist
'Education Thérapeutique' Instructor

Hughes Gauchez
President and founder of the association "Mucoviscidose et Kinésithérapie",
Representative for France at the IPGCF (International Physiotherapy group for CF)
Rehabilitation center manager for CF France
Autogenic Drainage instructor

Training Program tailored to your needs :

Theory
- Update on mucus knowledge
- Basis of airway clearance physiology
- Principles of autogenic drainage

Practice
- Simeox: principle and how to use it
- Review of patient cases

Hands-on and learning
- The role of the physiotherapist in coaching and supporting the patient

OUR EXPERIENCES WITH SIMEOX

PETRŐ Judit, BORKA Péter
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Cystic fibrosis is a genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR) that leads to malfunctioning of a small chloride channel. The disease is characterized by impaired mucociliary clearance and dehydration of airway surface liquid. As a result, microorganisms and other materials are not efficiently removed from the airways. Viscous secretions and persistent respiratory infections continuously damage the lung, which makes infection even more difficult to eradicate.
To treat this problem it is commonly used several inhale solutions like hypertonic saline or Pulmozyme, some expectoration technics and mucus clearance devices.
The cornerstone of cystic fibrosis treatment is to clear the extremely thick and sticky mucus from the airways.
With effective treatment it is able to prevent or decrease hyperinflation, atelectasis or the imbalance in ventilation moreover decrease the work of breathing. There are several airway clearance devices using the positive expiratory pressure with or without oscillation (Flutter, PEP, Acapella, Aerobica..)
A brand new equipment in this series is the **Physio-Assist Simeox.** The clearance session lasts between 20 - 30 minutes. The patient perform a set of passive and comfortable exhalations. During this Simeox provides vibratory signal to the patient's bronchial tree. This deconstruct the mucus to liquify it and act on its thixotropy. By changing the physical properties of mucus, Simeox helps mobilize secretions and transport for disposal.
We have the possibility to use the Physio-Assist Simeox in Korányi Hospital on Cystic Fibrosis department from October 2016. Most of the cases it is used during i.v. antibiotic treatment in inpatient period in less cases in outpatient treatment. Till this time 25 well-trained CF adult patients tried Simeox. The first cases were carried done together with the control of their physiotherapist. It was very important to teach them to a sigh type inspiration and to the relaxed, passive, and long expiration. Before the expectoration with Simeox our patients did their inhalation treatment to prepare their airways for cleaning. In this way the procedure was not so tedious but comfortable. At the beginning of usage the device we need to pay attention to teach our patients the relaxed exhalation especially who were not expertise in autogenic drainage. When they were able to carry out the proper exhalation the cleaning worked much more efficiently. Some patient had difficulties during the first some treatment especially those who tried to force the evacuation of the sputum. **The efficiency was the best at the patients who had a huge amount of sputum in their airways. They were able to expectorate more with less time.** Moreover they did not feel tiredness as with other techniques. Simeox was very useful with patients who had extremely thick and sticky mucus and this favorable effect lasted for hours after the treatment. Most of our patients used this airway clearance technique in a half sitting body position where they were able to relax absolutely others used it in sitting position and a few patients were in side lying. Only two patients of our were not able to accept the Simeox. One of these two insist on his earlier technique the other had difficulties to position her language.
Our patients would prefer the Simeox for their everyday treatment at home and not only at the CF department.