UMC Utrecht

Cystic Fibrosis

2025

Prof dr Harry Heijerman, Pulmonologist
UMC Utrecht

Sweat and CF

Dorothy Andersen (1901-1963)

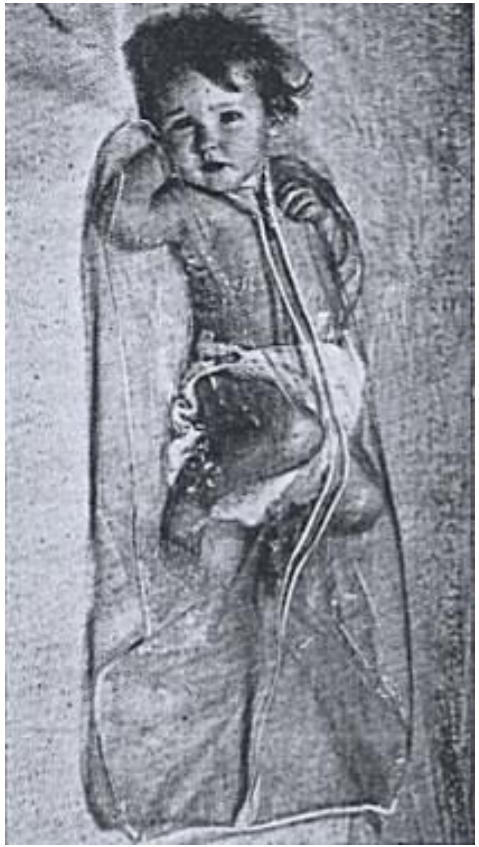
1938: Fibrocystic disease of the Pancreas

HEAT PROSTRATION IN FIBROCYSTIC DISEASE OF THE PANCREAS AND OTHER CONDITIONS

By WALTER R. KESSLER, M.D., PH.D., AND DOROTHY H. ANDERSEN, M.D., MED.SC.D.
New York City

DURING the heat wave which occurred in New York City in August 1948, seven children were seen at the Babies Hospital within a space of 24 hours and three more within the week who presented a similar clinical picture. This was manifested by a sudden onset, after approximately 48 hours of hot weather, of marked dehydration, fever and signs of circulatory collapse in the absence of any obvious clinical evidence of acute infection. The major portion of this group was composed of patients who had been previously studied at Babies Hospital and in whom the diagnosis of cystic fibrosis of the pancreas had been established. It is of more than passing interest that one of the patients with heat prostration was found to have previously unsuspected fibrocystic disease.

Pediatrics 1951



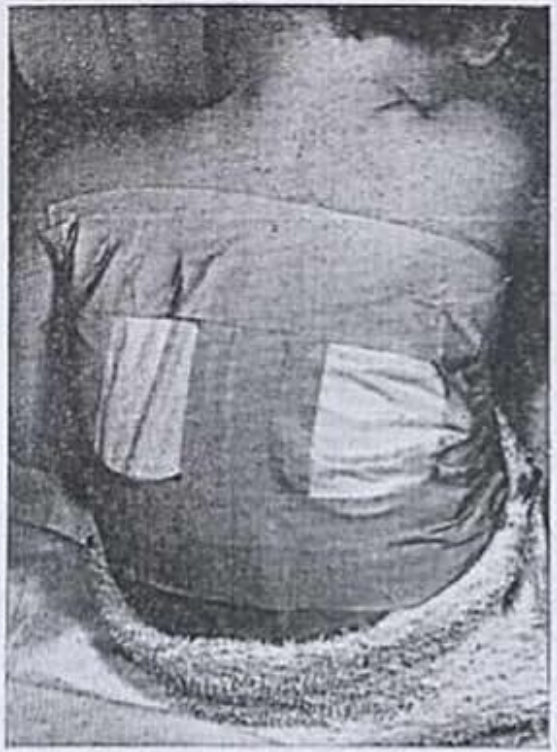


FIG. 2.—Mode of attachment of filter papers and plastic strips to child.

1953
Paul Di’Agnese

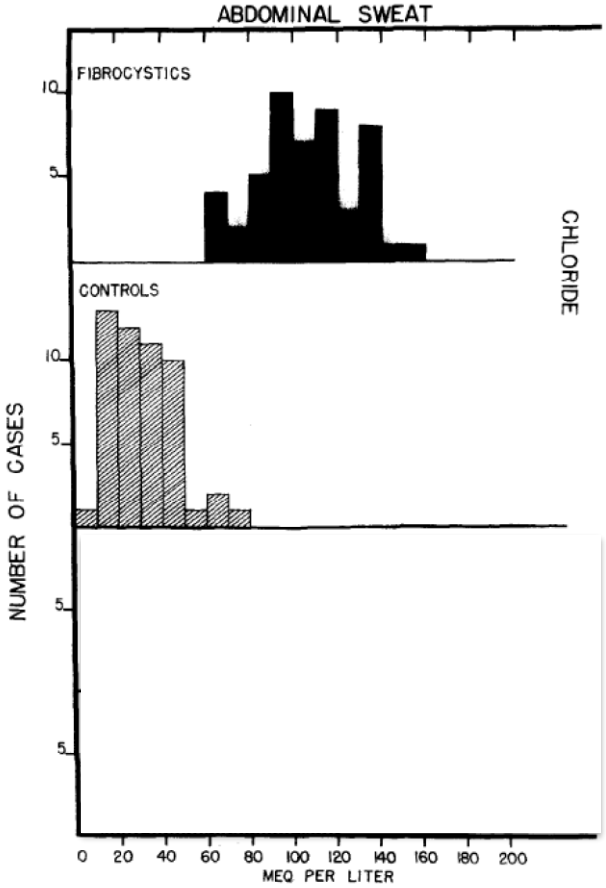
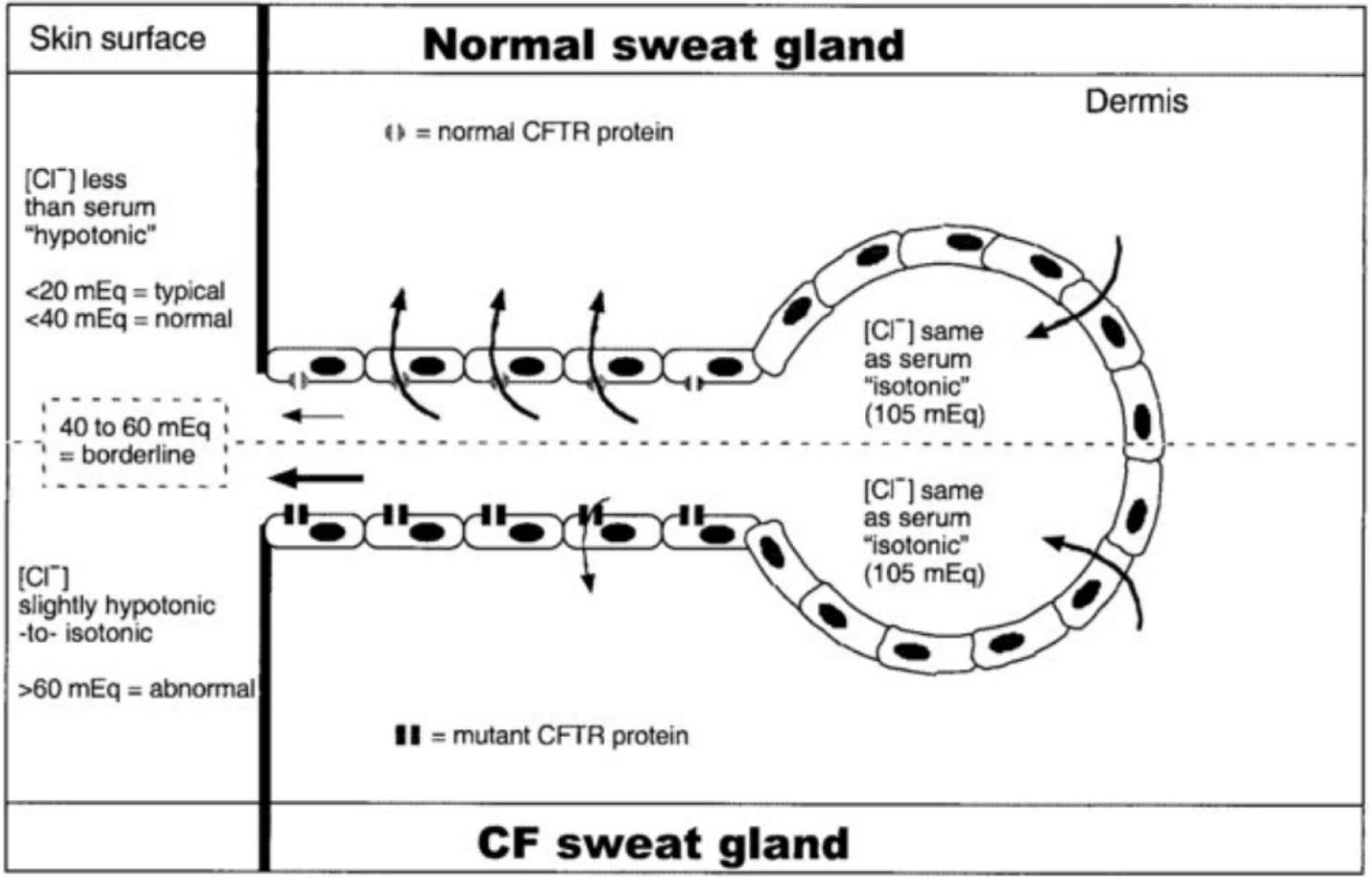


FIG. 1. Abdominal sweat chloride and sodium in patients with fibrocystic disease of the pancreas and in control cases representing a variety of other types of diseases.


Skin surface
Normal sweat gland
Dermis
= normal CFTR protein
[Cl⁻] less than serum "hypotonic"
<20 mEq = typical
<40 mEq = normal
40 to 60 mEq = borderline
[Cl⁻] slightly hypotonic -to- isotonic
>60 mEq = abnormal
[Cl⁻] same as serum "isotonic" (105 mEq)
[Cl⁻] same as serum "isotonic" (105 mEq)
= mutant CFTR protein
CF sweat gland

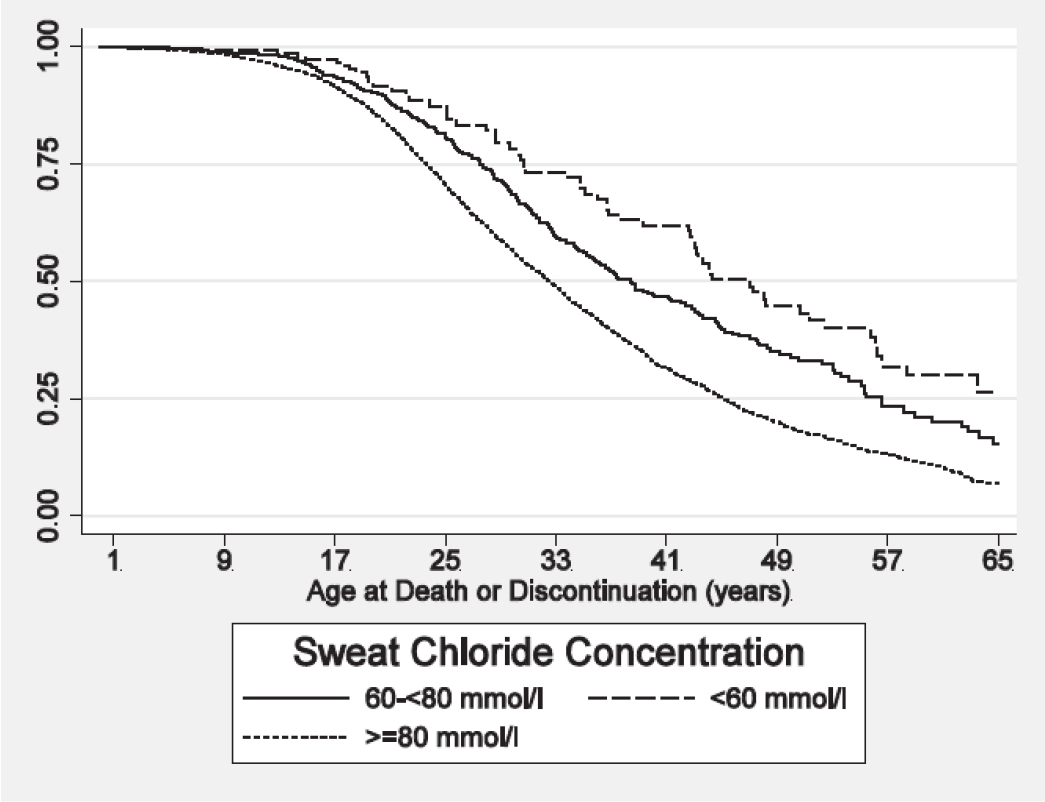
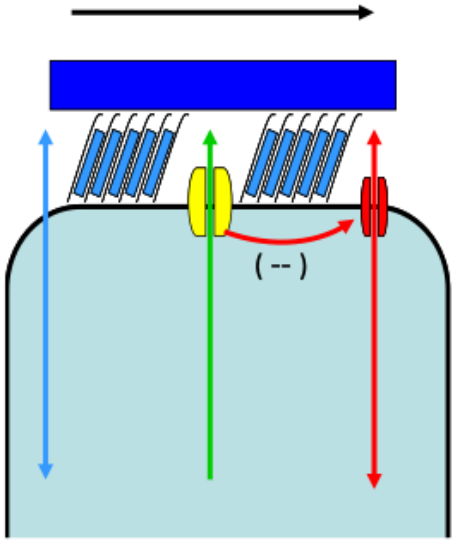


Fig. 1. Mortality according to level of sweat chloride at baseline.

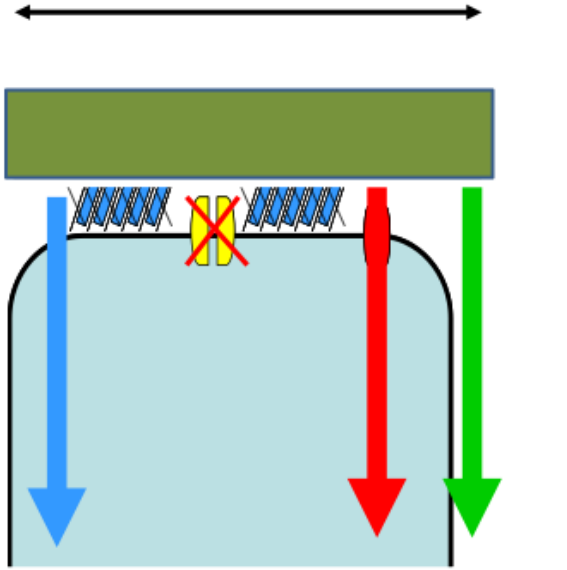
Age at diagnosis:

> 80 mmol/L: 2,9 yrs
60-80 mmol/L: 8,3 yrs
< 60 mmol/L: 11,1 yrs

McKone JCF 2015

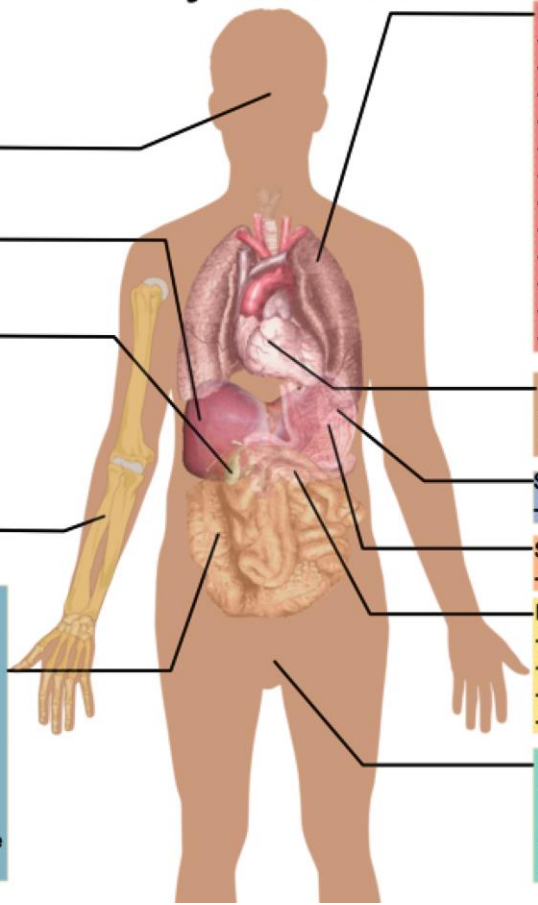


Normal



Cystic Fibrosis

Manifestations of Cystic Fibrosis



General
- Growth failure (malabsorption)
- Vitamin deficiency states (vitamins A, D, E, K)

Nose and sinuses
- Nasal polyps
- Sinusitis

Liver
- Hepatic steatosis
- Portal hypertension

Gallbladder
- Biliary cirrhosis
- Neonatal obstructive jaundice
- Cholelithiasis

Bone
- Hypertrophic osteoarthropathy
  - Clubbing
- Arthritis
- Osteoporosis

Intestines
- Meconium ileus
- Meconium peritonitis
- Rectal prolapse
- Intussusception
- Volvulus
- Fibrosing colonopathy (strictures)
- Appendicitis
- Intestinal atresia
- Distal intestinal obstruction syndrome
- Inguinal hernia

Lungs
- Bronchiectasis
- Bronchitis
- Bronchiolitis
- Pneumonia
- Atelectasis
- Hemoptysis
- Pneumothorax
- Reactive airway disease
- Cor pulmonale
- Respiratory failure
- Mucoid impaction of the bronchi
- Allergic bronchopulmonary aspergillosis

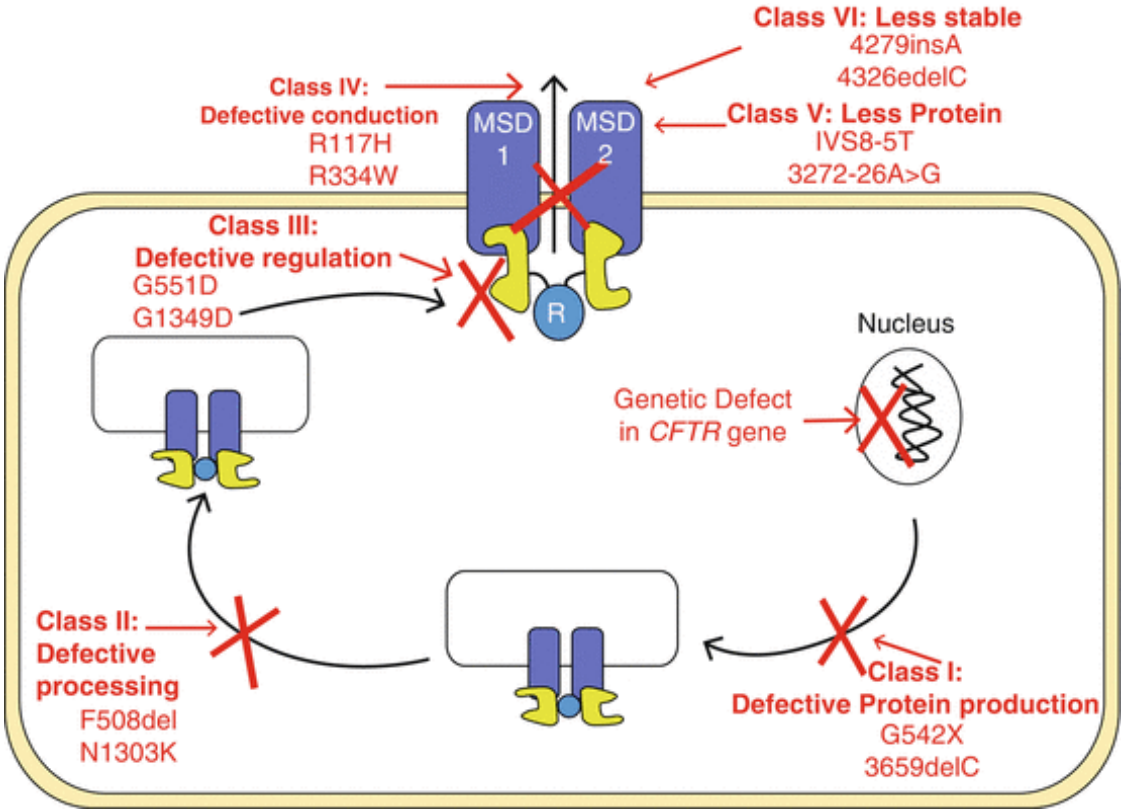
Heart
- Right ventricular hypertrophy
- Pulmonary artery dilation

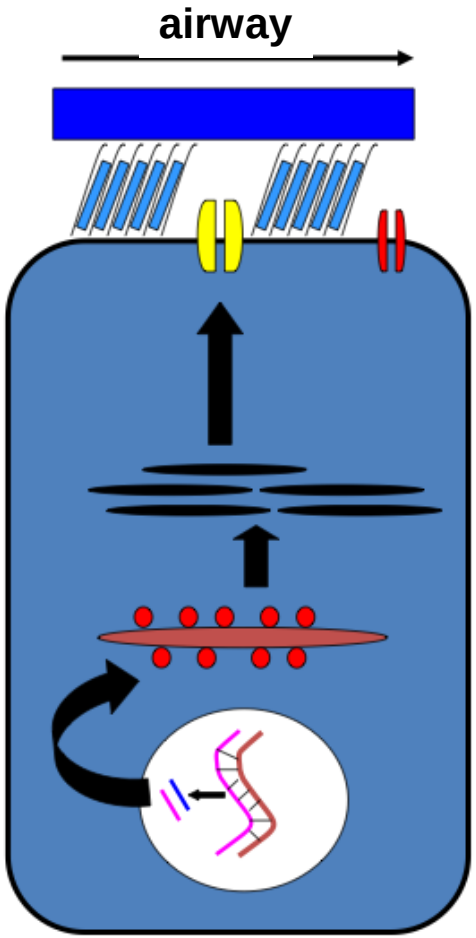
Spleen
- Hypersplenism

Stomach
- GERD

Pancreas
- Pancreatitis
- Insulin deficiency
- Symptomatic hyperglycemia
- Diabetes

Reproductive
- Infertility (aspermia, Absence of vas deferens)
- Amenorrhea
- Delayed puberty


Class VI: Less stable
4279insA
4326delC
Class IV:
Defective conduction
R117H
R334W
MSD 1
MSD 2
Class V: Less Protein
IVS8-5T
3272-26A>G
Class III:
Defective regulation
G551D
G1349D
R
Nucleus
Genetic Defect
in CFTR gene
Class II:
Defective
processing
F508del
N1303K
Class I:
Defective Protein production
G542X
3659delC



1. : Potentiator
   - Ivacaftor (Kalydeco)
   - Deutivacaftor

2. : Corrector
   - Lumacaftor
   - Tezacaftor
   - Elexacaftor
   - Vanzacaftor

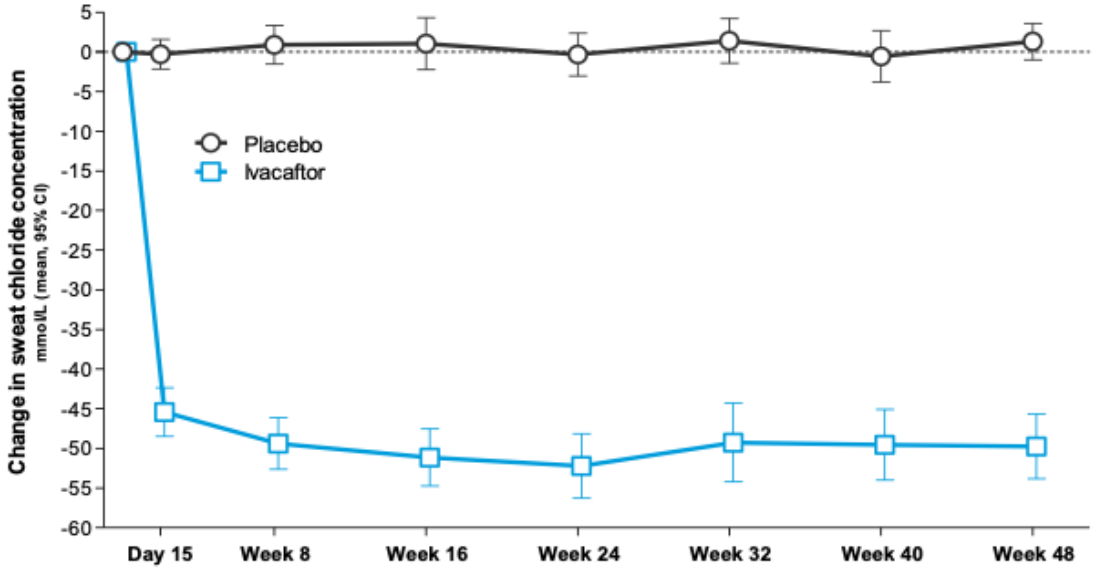
3. : Amplifier
   - PTI 428

4. : Read Through
   - ELX-02

1.	Kopiëren	Negeert vroegtijdige stopper (overschrijver)

Class III

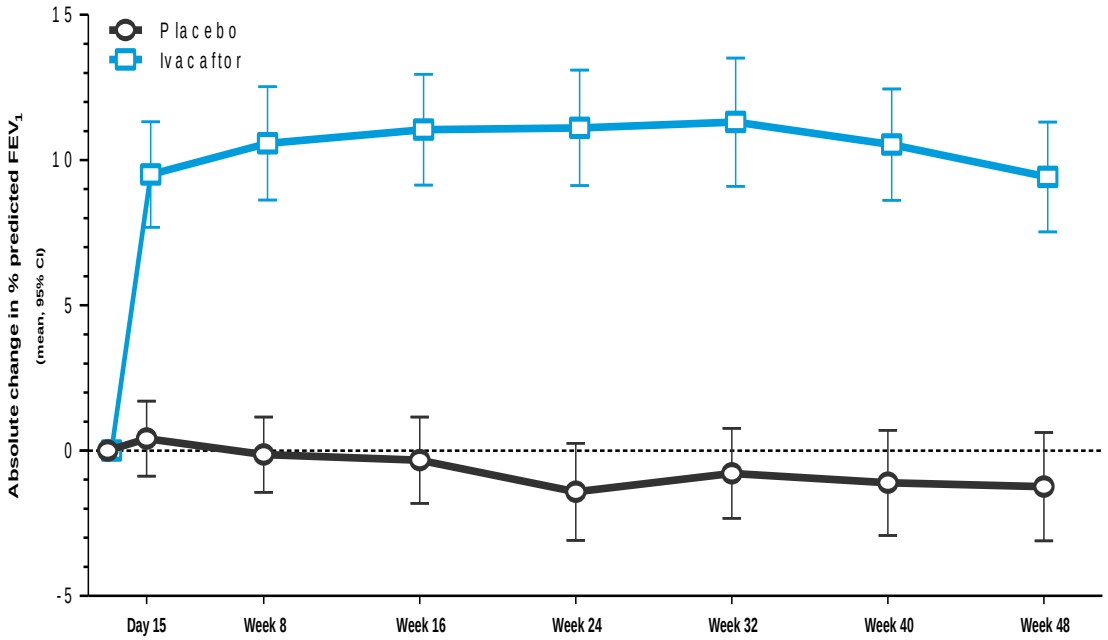
Ivacaftor (Kalydeco), Change in Sweat Test



Ramsey et al., N Engl J Med. 2011 Nov 3;365(18):1663-72

Class III

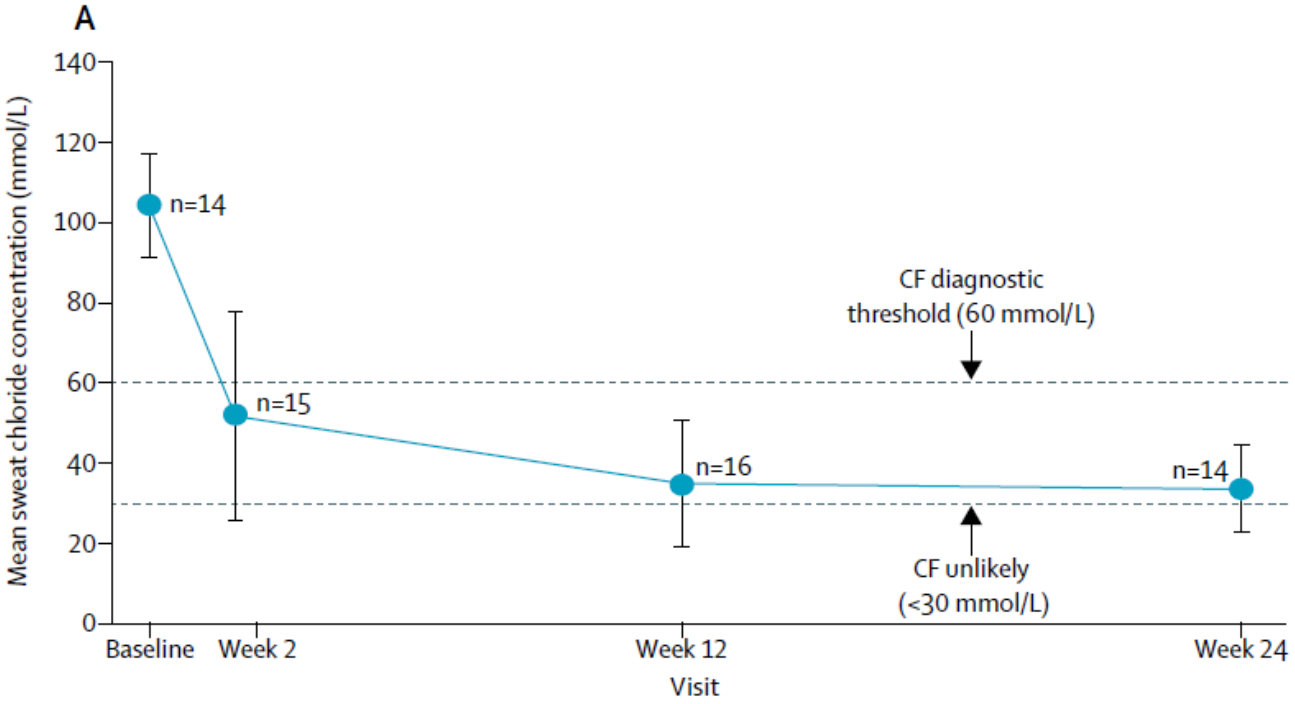
Ivacaftor (Kalydeco), Change in Lung Function



Ramsey et al., N Engl J Med. 2011 Nov 3;365(18):1663-72

Class III

Ivacaftor in 12-24 month infants
Sweat test

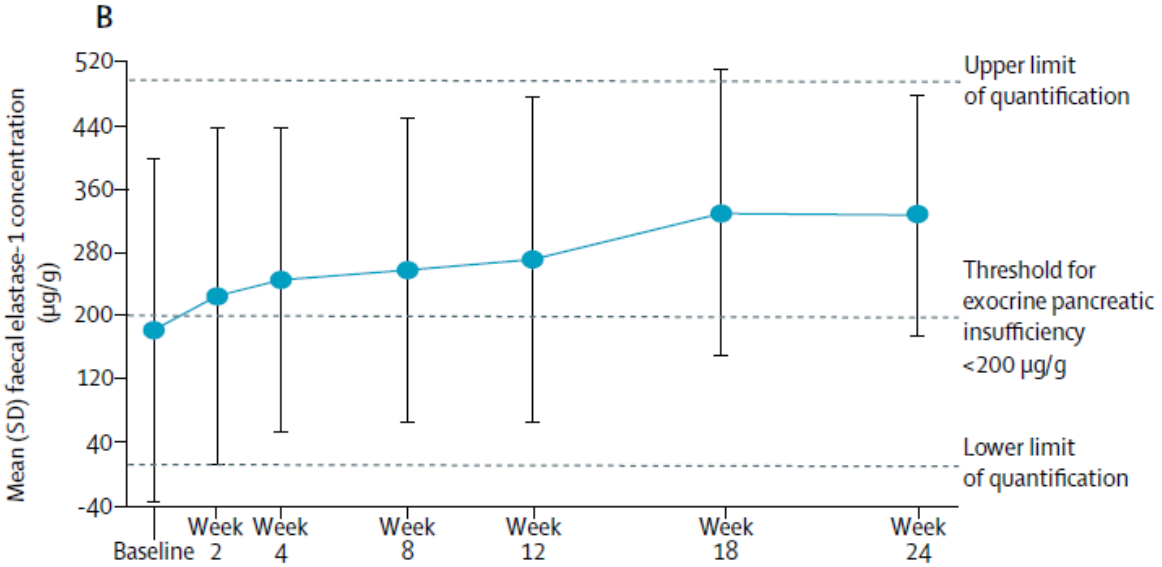


Rosenfeld Lancet Resp Med 2018

Class III

Ivacaftor in children 12-24 months

Pancreatic Function

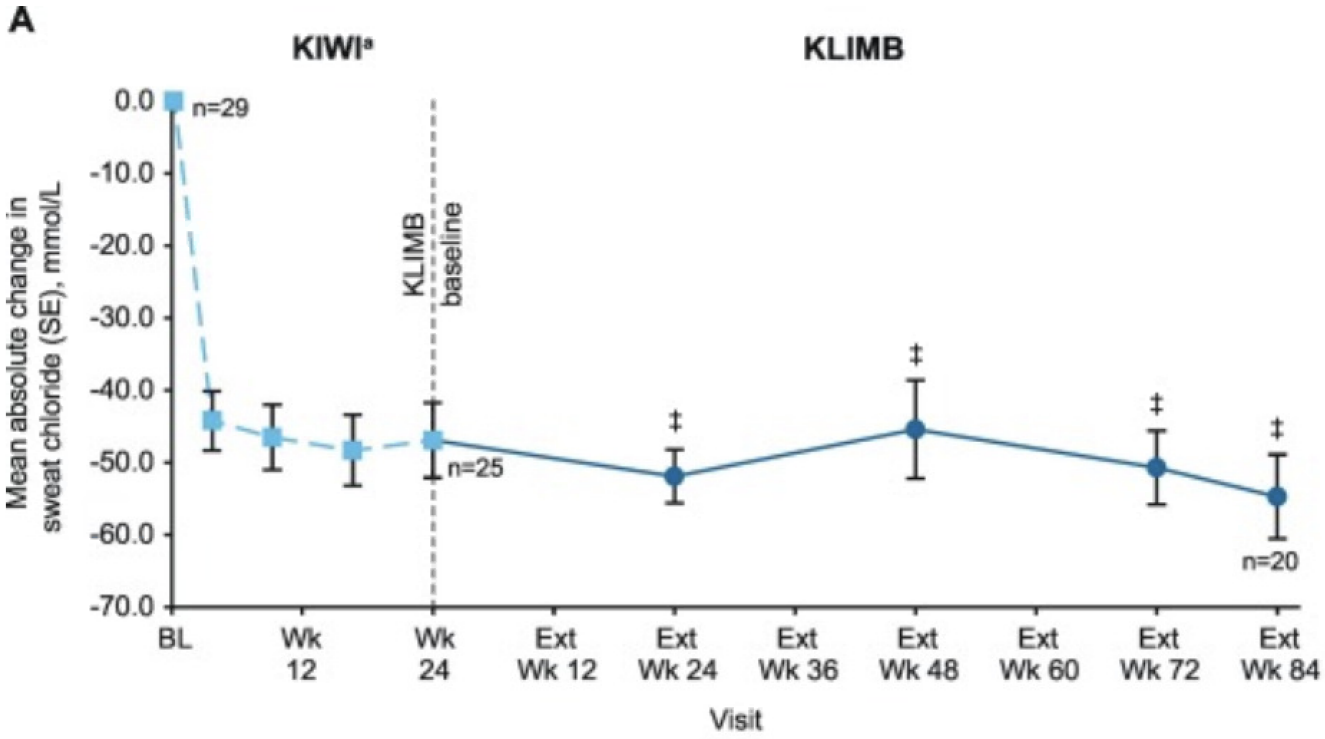


Rosenfeld Lancet Resp Med 2018

Class III

Ivacaftor in children 2-5 years

Sweat test

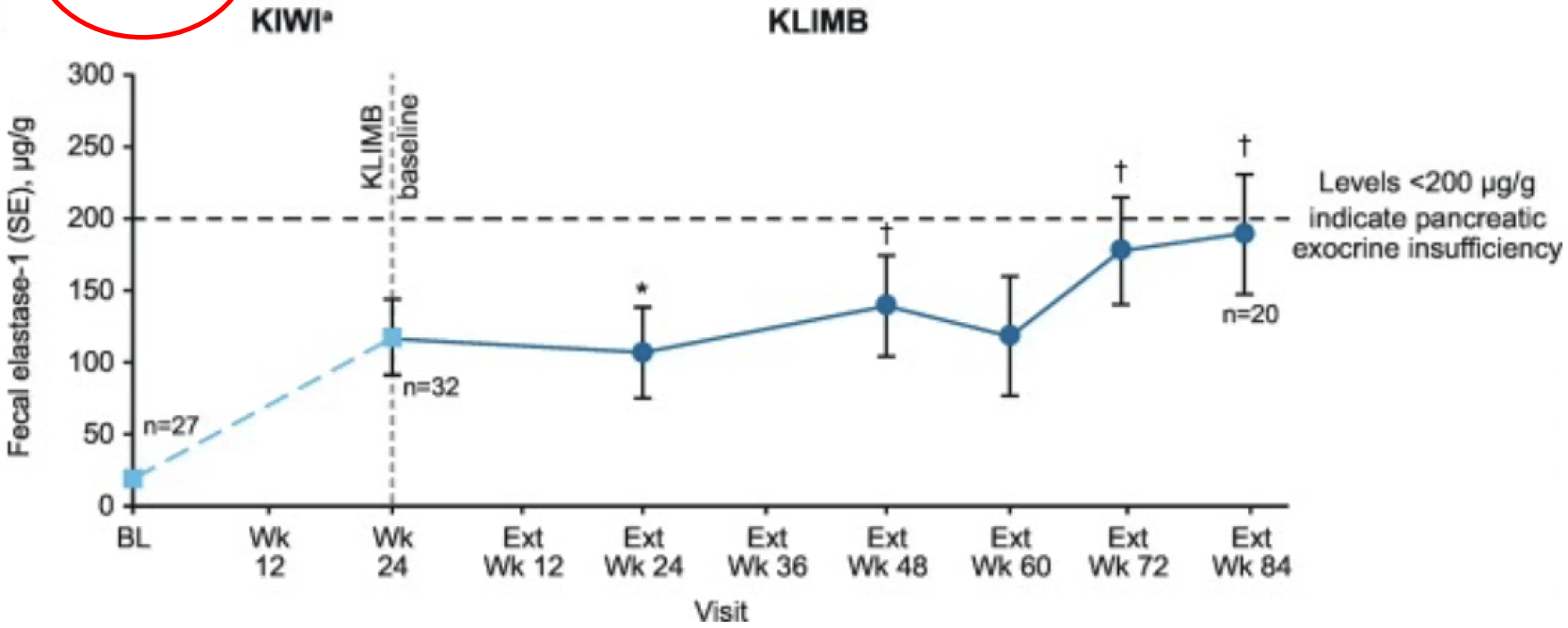


Rosenfeld et al JCF 2019

Ivacaftor in children 2-5 years

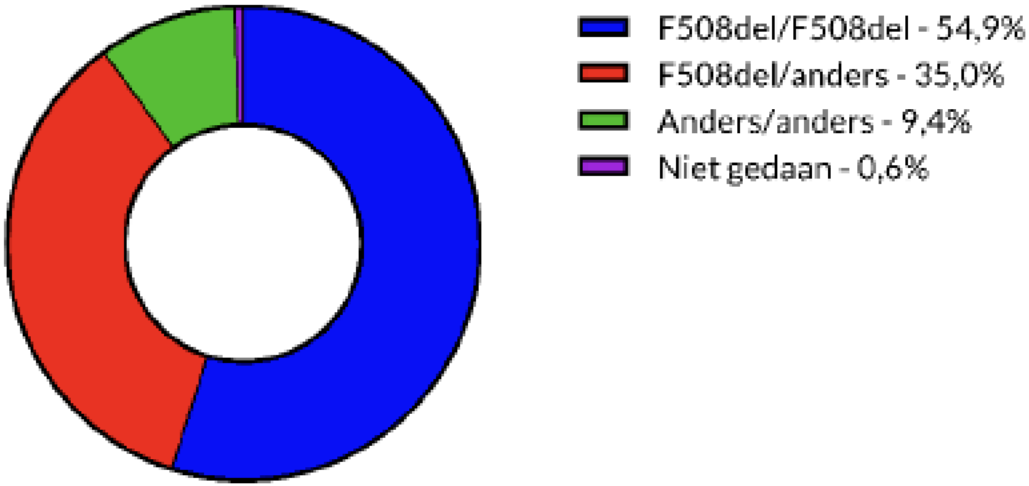
Class III

Pancreatic Function



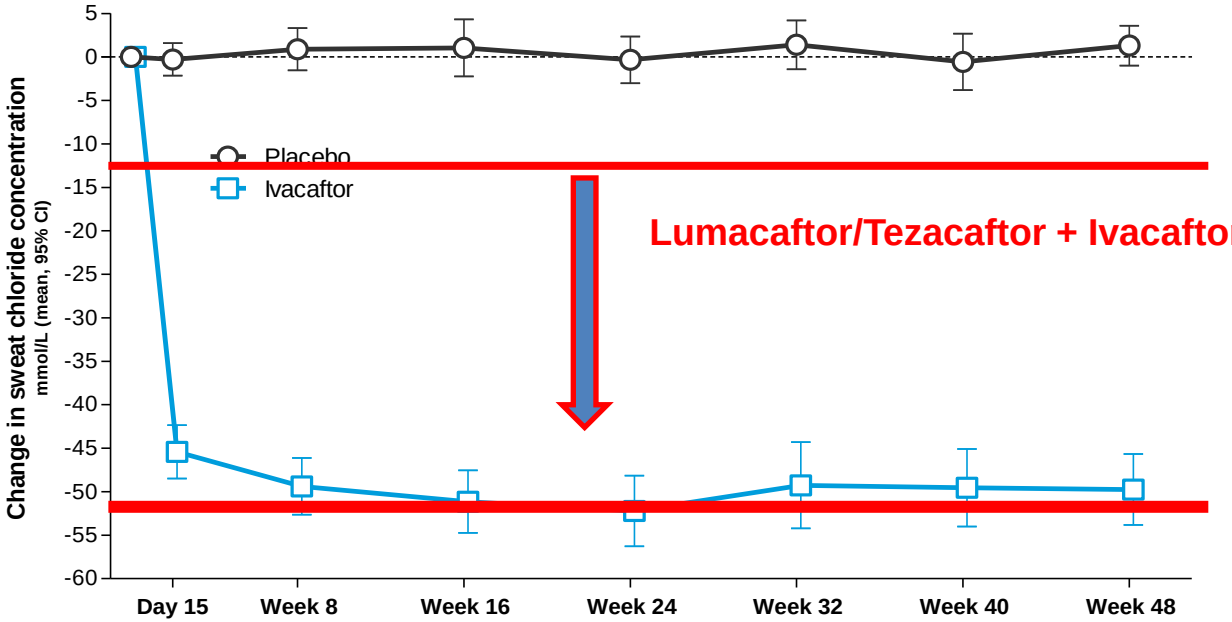
Rosenfeld et al JCF 2019

F508del is most frequent CFTR mutation.



Dutch CF registration 2021

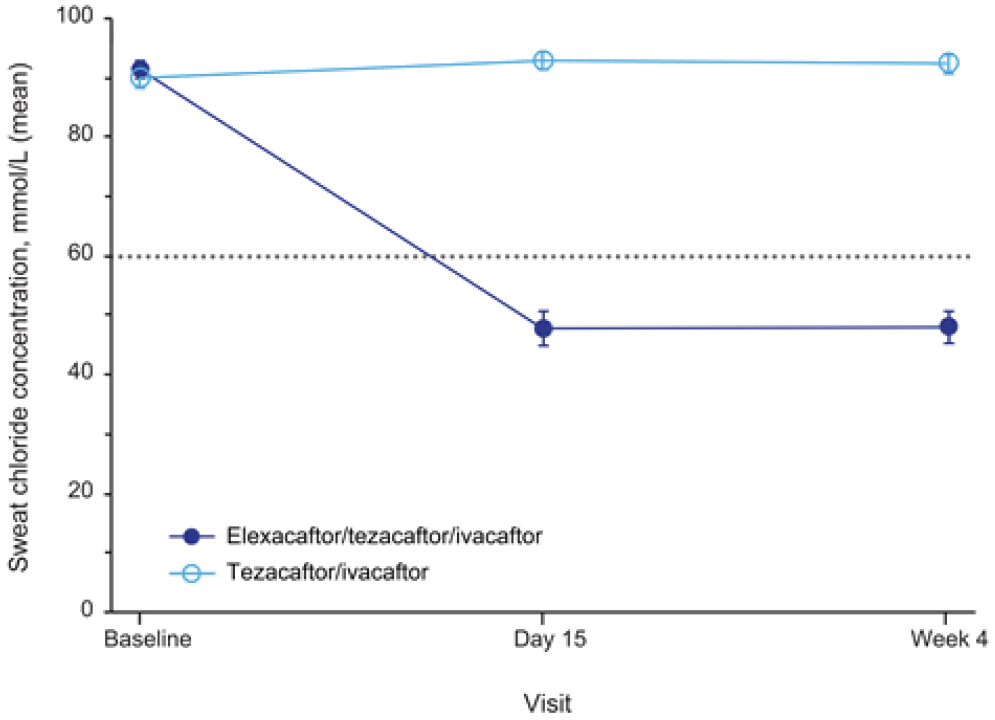
Effect of CFTR modulators in dF508/dF508



Lumacaftor/Tezacaftor + Ivacaftor in dF508/dF508

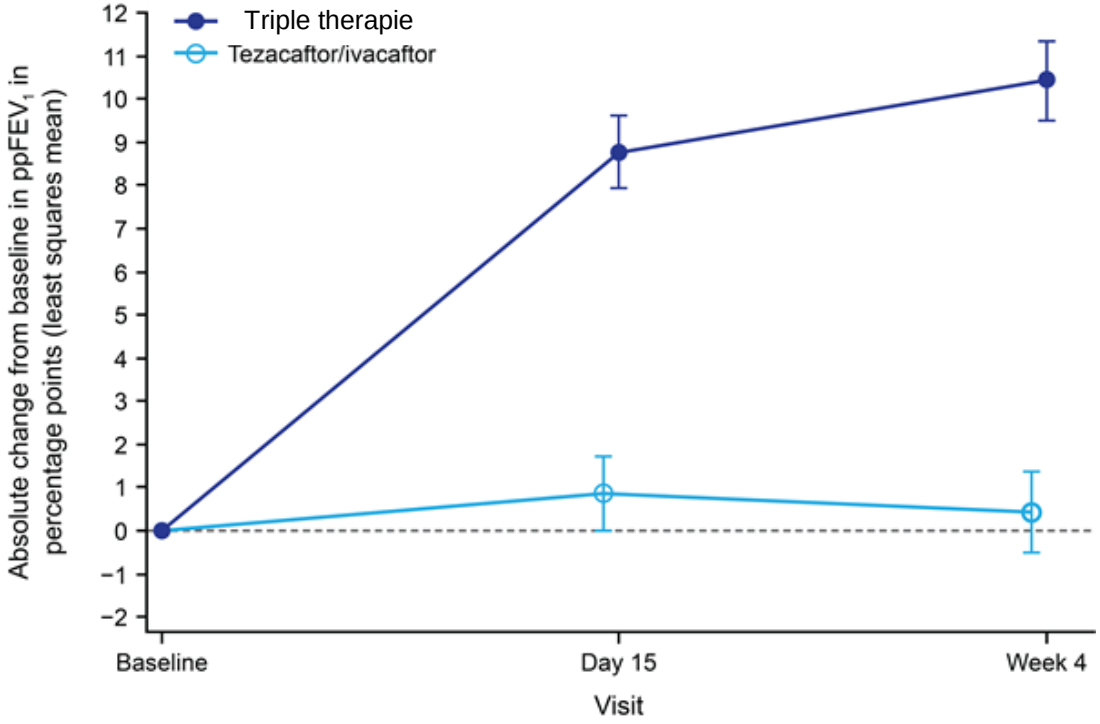
Tezacaftor/Ivacaftor/Elexacaftor in dF508/dF508

Sweat Chloride



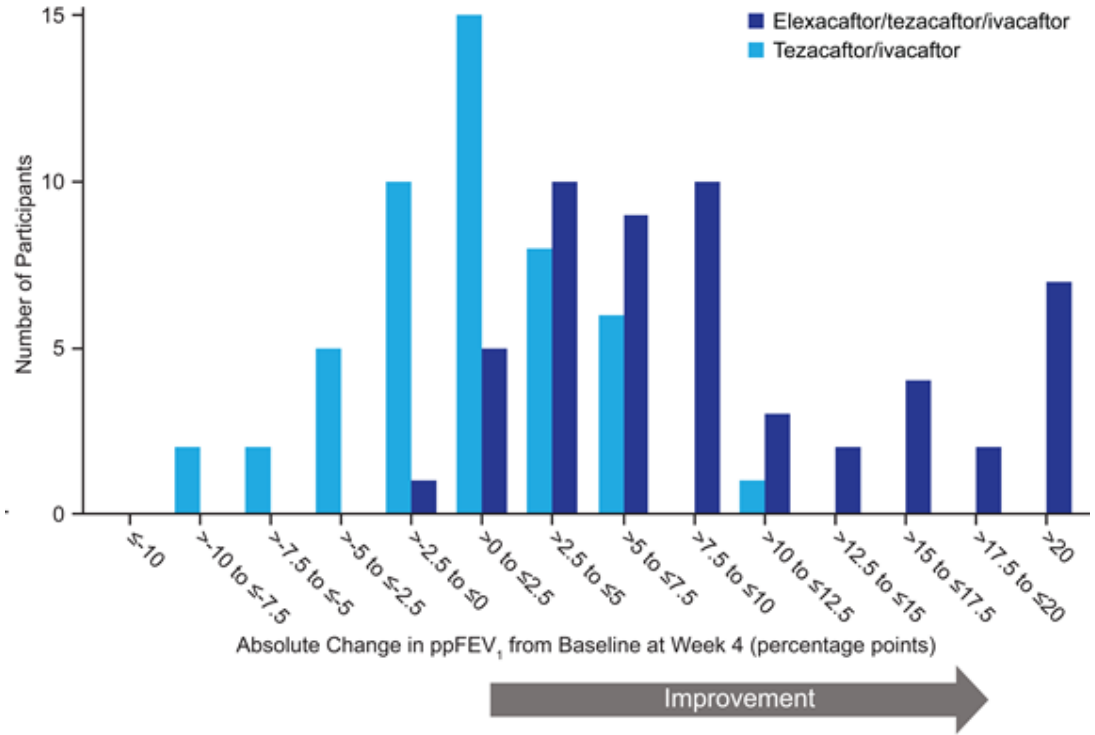
Heijerman et al Lancet 2019

Elexacaftor/Tezacaftor/Ivacaftor bij dF508/dF508
Lung Function



Heijerman et al Lancet 2019

Tezacaftor/Ivacaftor/Elexacaftor in dF508/dF508



Heijerman et al Lancet 2019

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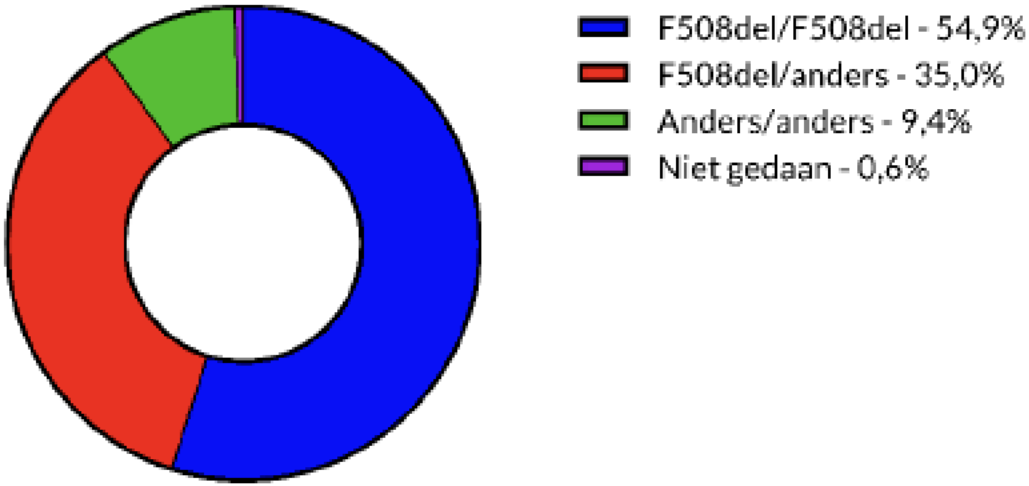
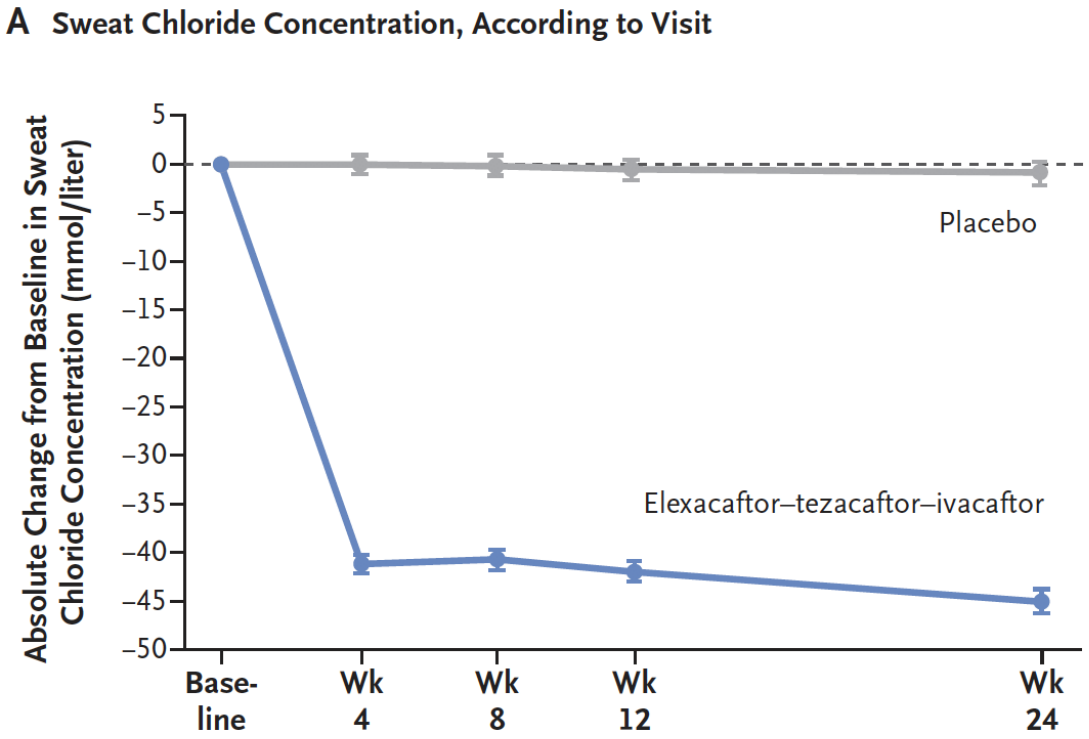


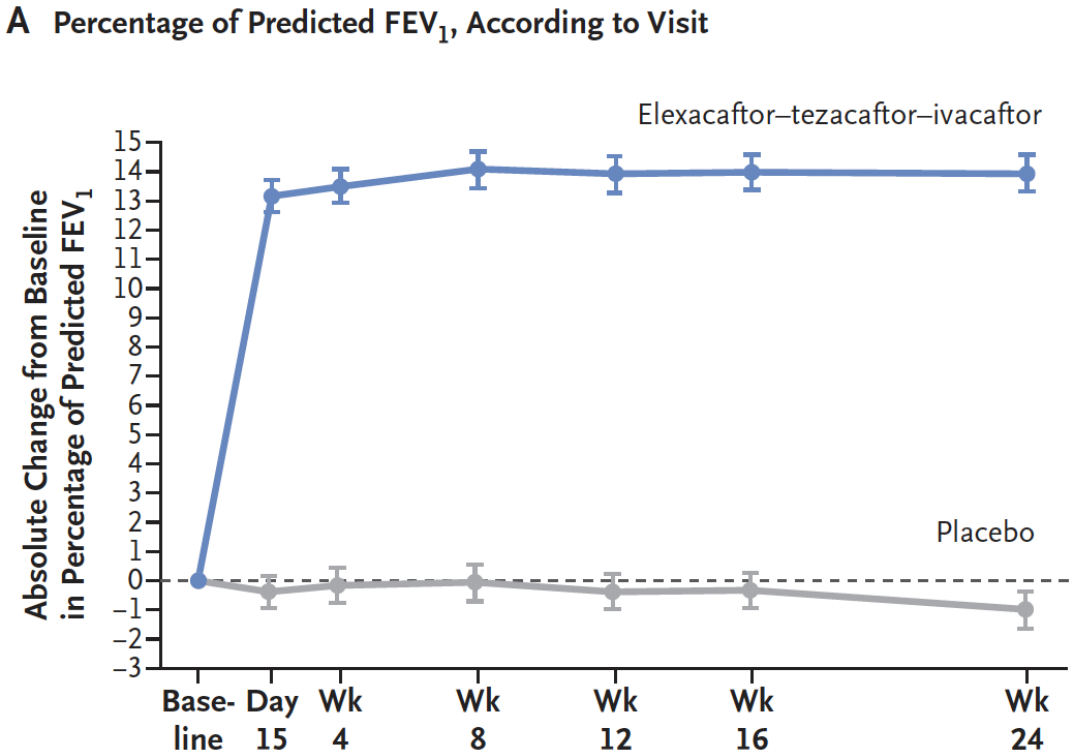
Dutch CF registry 2018

Elexacaftor/Tezacaftor/Ivacaftor in patients with 1 F508del mutation and a minimal function mutation



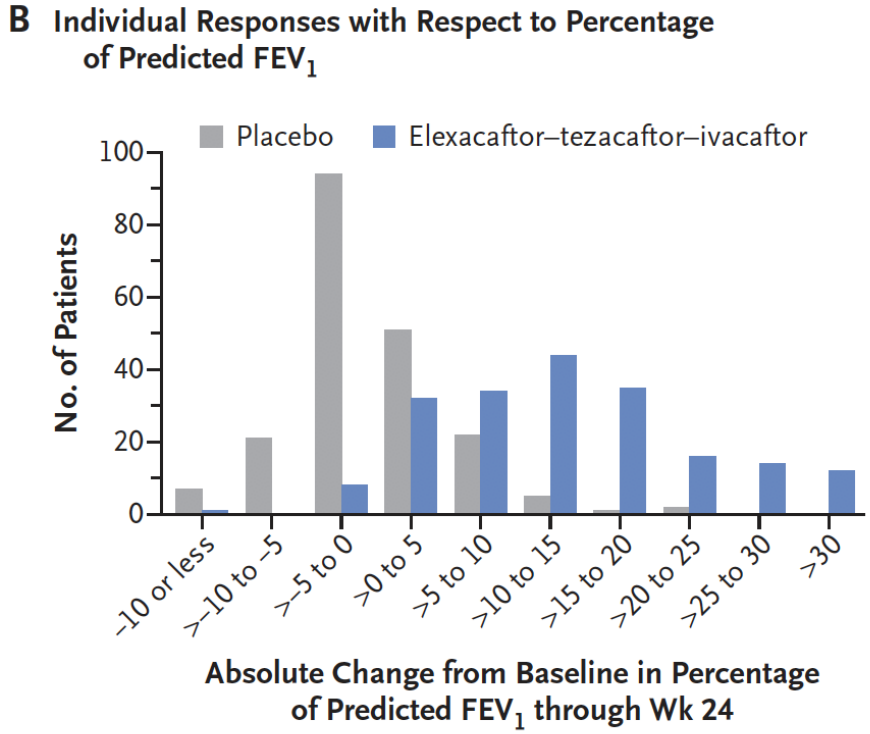
Middleton et al NEJM 2019

Elexacaftor/Tezacaftor/Ivacaftor in patients with 1 F508del mutation and a minimal function mutation



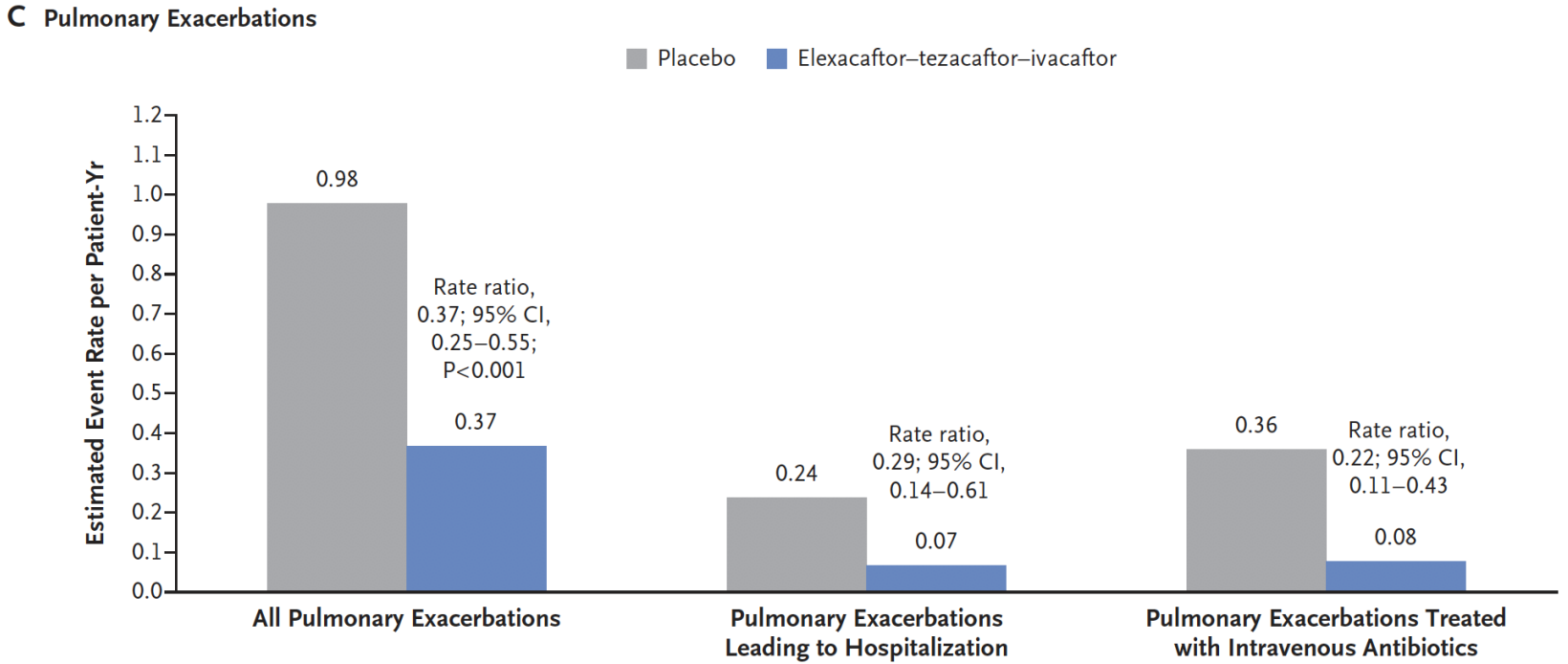
Middleton et al NEJM 2019

Elexacaftor/Tezacaftor/Ivacaftor in patients with 1 F508del mutation and a minimal function mutation

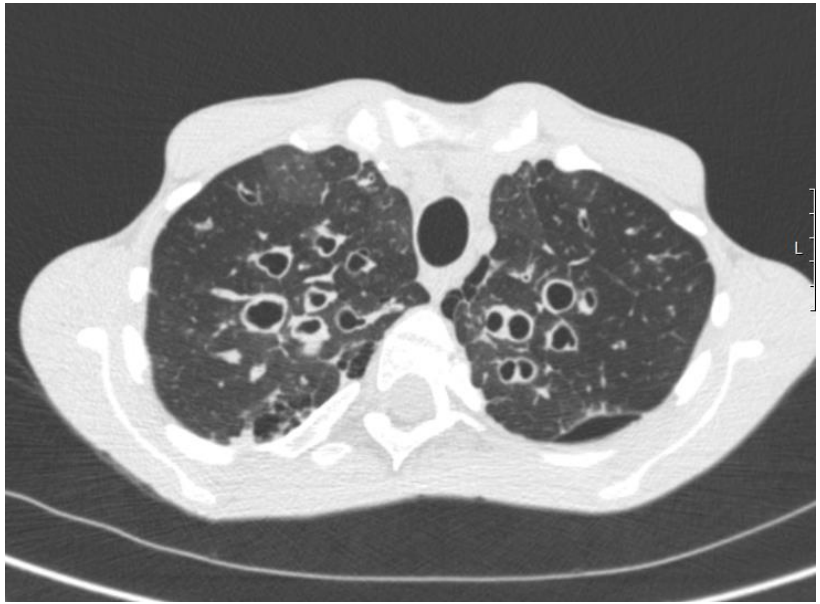


Middleton et al NEJM 2019

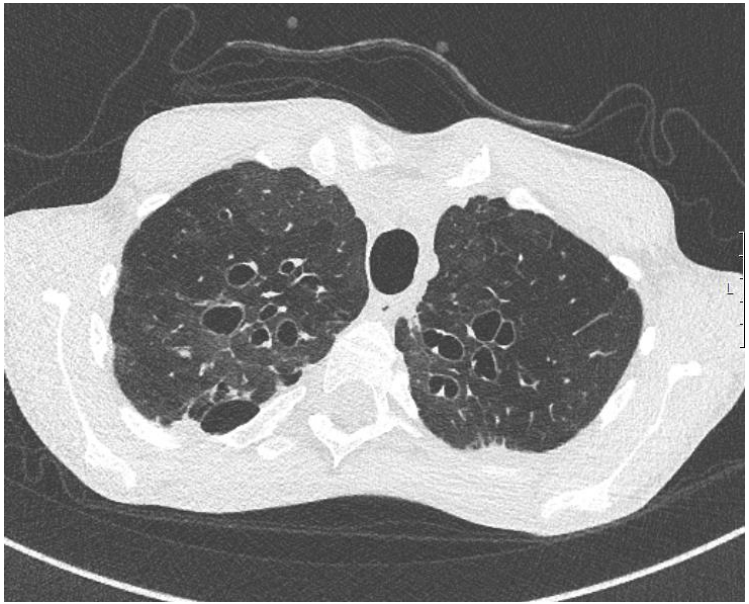
Elexacaftor/Tezacaftor/Ivacaftor in patients with 1 F508del mutation and a minimal function mutation



Middleton et al NEJM 2019



SwCl: 89 mmol/L

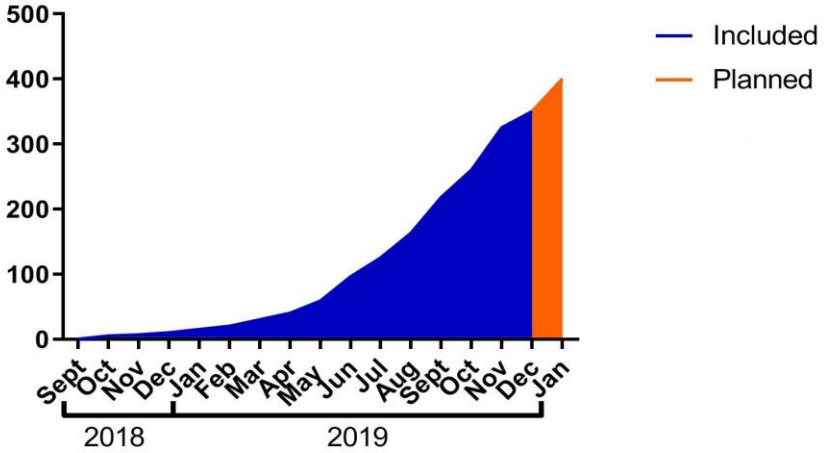


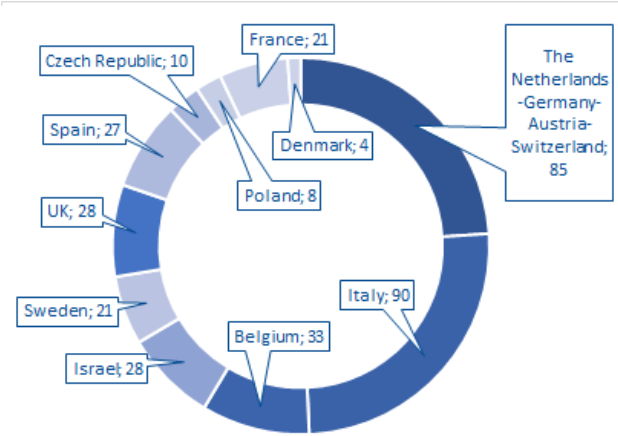
SwCl: 32 mmol/L

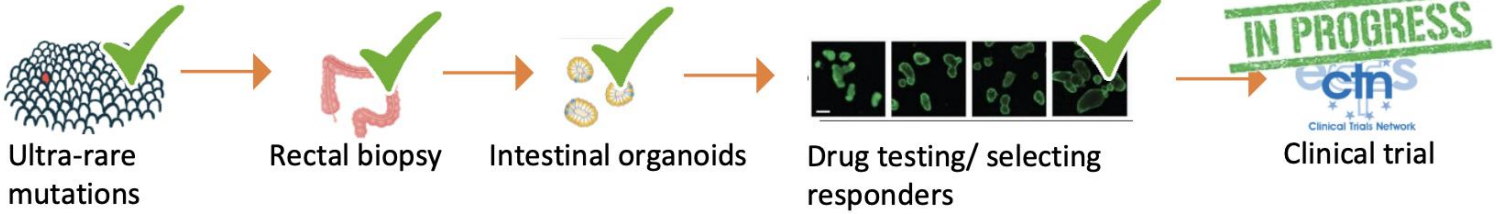
Effect Kaftrio in Nederland na 6 maanden behandeling.

	Pre			Post			Paired samples		
	N	Mean	SD	N	Mean	SD	N	Mean change	Paired t-test
FEV1%pred GLI	713	70.4	22.2	536	81.0	22.6	535	11.9	<0.001
BMI kg/m^2	740	21.6	3.5	546	22.1	3.0	545	0.9	<0.001
Sweat chloride (mmol/L)	562	85.8	21.3	249	38.3	19.0	229	-49.4	<0.001
CFQ-R respiratory	598	70.8	19.4	380	89.4	11.8	344	19.6	<0.001
CFQ-R digestive	598	76.8	19.4	380	79.2	16.6	343	1.5	0.115

And the remaining 10% of all patients
HIT-CF Europe project



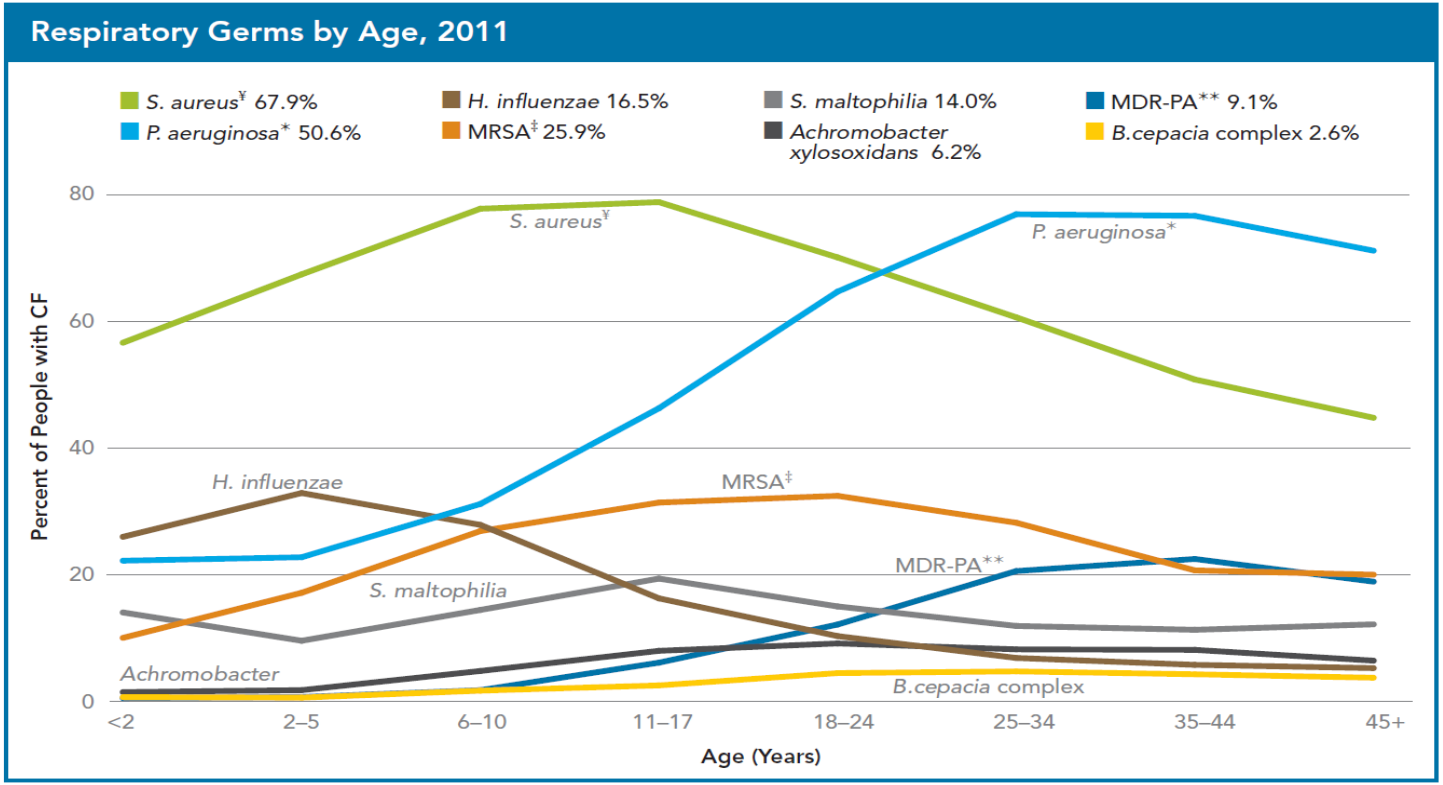




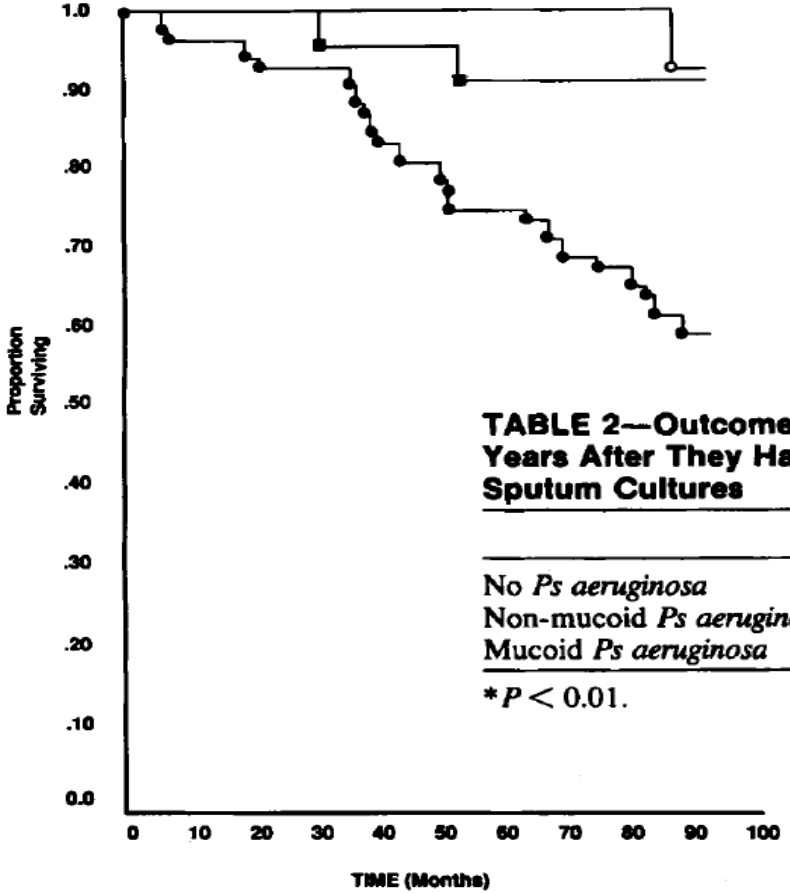
Ultra-rare mutations → Rectal biopsy → Intestinal organoids → Drug testing/ selecting responders → Clinical trial

Microbiologie: infecties en behandeling

Respiratory Germs by Age, 2011



Survival related to results of sputum culture



1980 - 1988

TABLE 2—Outcome of Patients (Dead or Alive) Eight Years After They Had Been Classified According to Sputum Cultures

	Alive*	Dead	(%)
No *Ps aeruginosa*	11	1	(8)
Non-mucoid *Ps aeruginosa*	17	2	(11)
Mucoid *Ps aeruginosa*	29	21	(42)

*$P < 0.01$.

Henry et al. Pediatr Pulmonol 1992

Determinants of Mortality from Cystic Fibrosis in Canada, 1970–1989

Corey and Farewell Am J Epidemiol 1996

TABLE 5. Proportional hazards models of Canadian cystic fibrosis mortality for the period 1985–1989, when clinical variables were measured n 3795

Model	Variable	Hazard ratio	95% confidence interval
1	Sex, female vs. male	1.73***	1.26–2.38
2	FEV_1†, % predicted	0.93***	0.92–0.94
3	Weight, % predicted	0.95***	0.93–0.96
4	*P. aeruginosa*†	2.07***	1.37–3.13
5	*B. cepacia*†	3.22***	2.33–4.46

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

† FEV_1, forced expiratory volume in one second; *P. aeruginosa*, *Pseudomonas aeruginosa*; *B. cepacia*, *Burkholderia cepacia*.

Impact of *Pseudomonas and Staphylococcus Infection on Inflammation and* Clinical Status in Young Children with Cystic Fibrosis

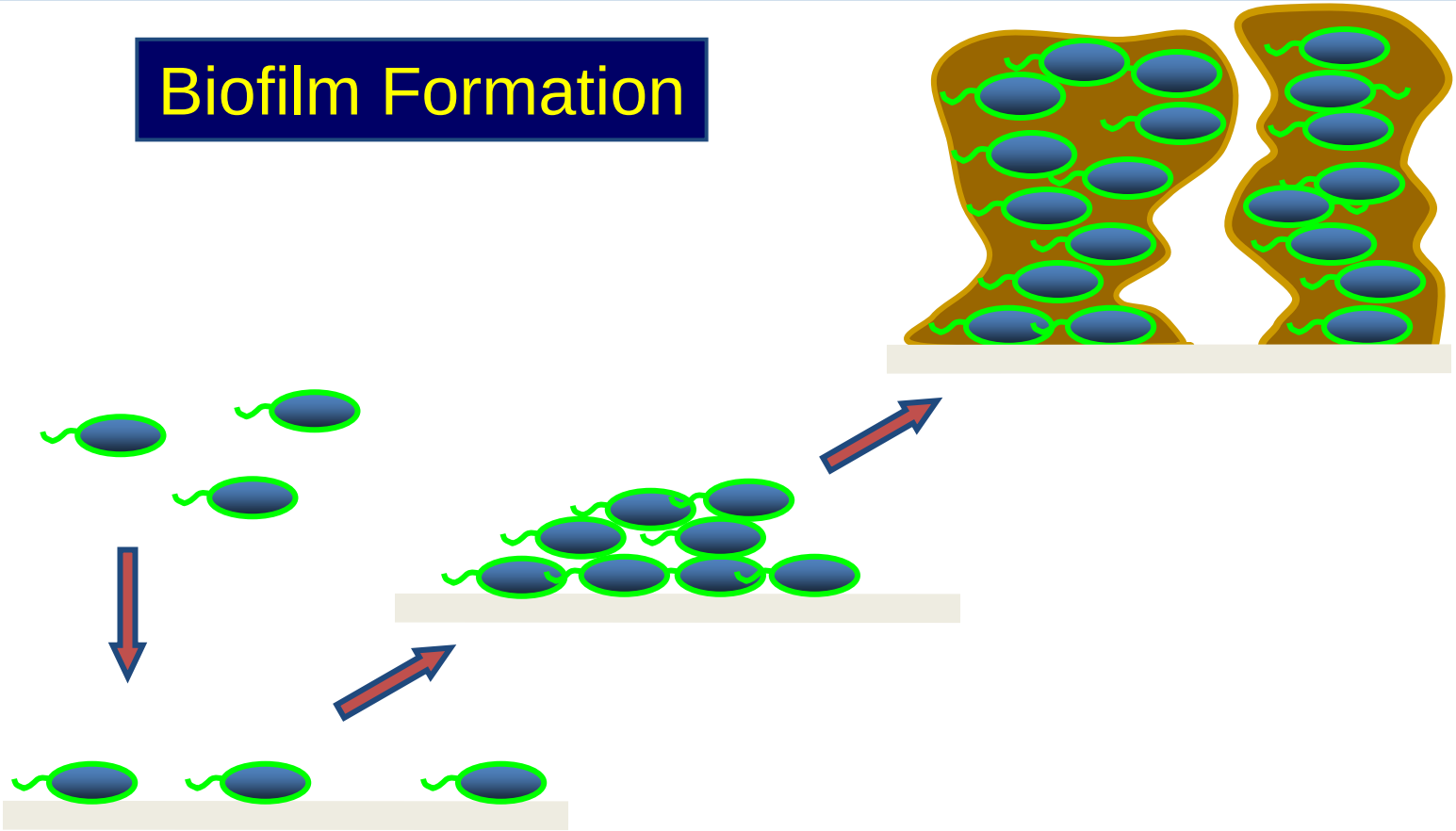
111 children age < 6 years who had 2 *P aeruginosa–positive oropharyngeal cultures within 12* months.

Table III. BALF inflammatory markers by study group

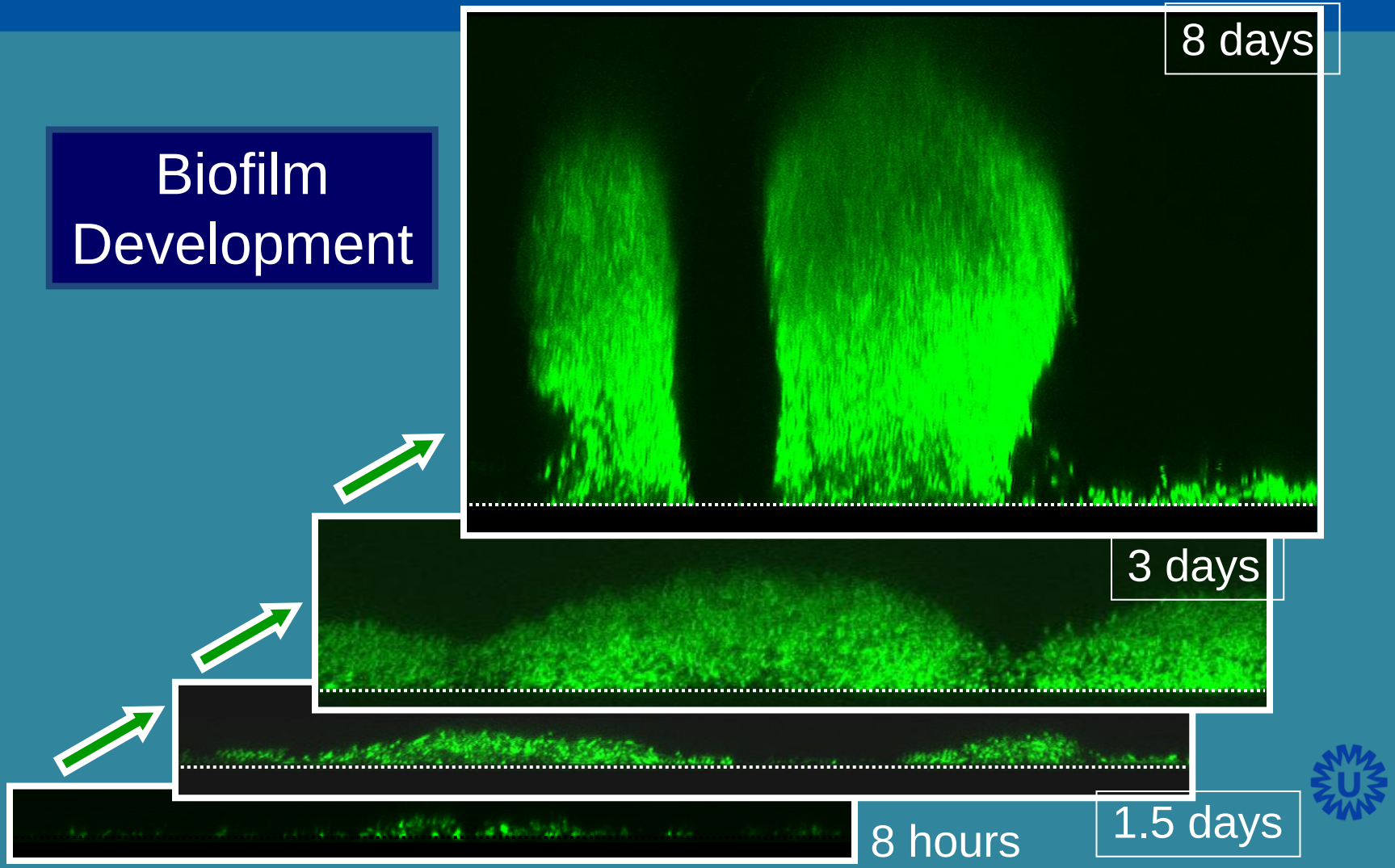
	BAL-negative for all CF bacterial pathogens (n = 31)	BAL *P aeruginosa*–negative but other pathogens positive (n = 21)	BAL *P aeruginosa*–positive (n = 59)	*P* value
Log_{10} total white cells, per mL	5.6 (0.3)	5.9 (0.3)*	6.0 (0.4)†	<.0001
Log_{10} neutrophils, per mL	4.8 (0.6)	5.4 (0.5)†	5.6 (0.7)†	<.0001
Percent neutrophils	22.1 (14.4)	33.6 (17.6)‡	49.3 (25.9)†§	<.0001
Log_{10} IL-8, pg/mL	2.3 (0.6)	2.8 (0.7)*	3.1 (0.6)†	<.0001
Log_{10} IL-6, pg/mL	0.9 (0.5)	1.2 (0.5)	1.2 (0.5)	.06
Neutrophil elastase detected¶	0/30 (0.0%)	3/21 (14.3%)	23/56 (41.1%)	<.001

Sagel et al. J Pediatr 2009;154:183-8

Biofilm Formation



Biofilm Development



What we know:

Chronic infection with Pseudomonas aeruginosa leads to::

A more rapid decline in lung function

- An increase in hospital admissions (and in-hospital days)
- A decreasee in life expectancy

Chronic infection with an epidemic strain of Pseudomonas leads to:

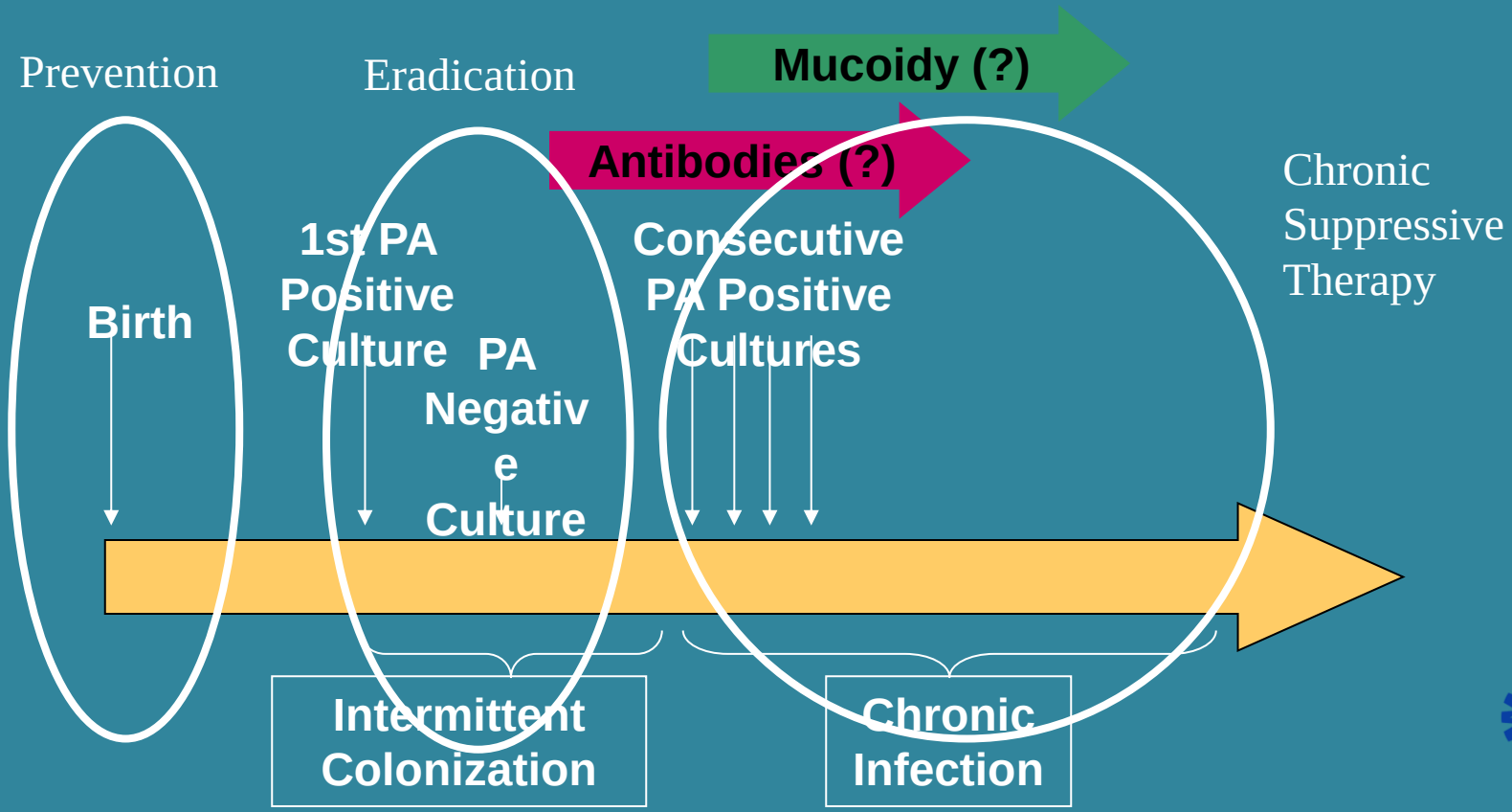
- An increase in antimicrobial resistance
- An increase in morbidity (hospital admissions)
- A more rapid decline in lung function

Prevention

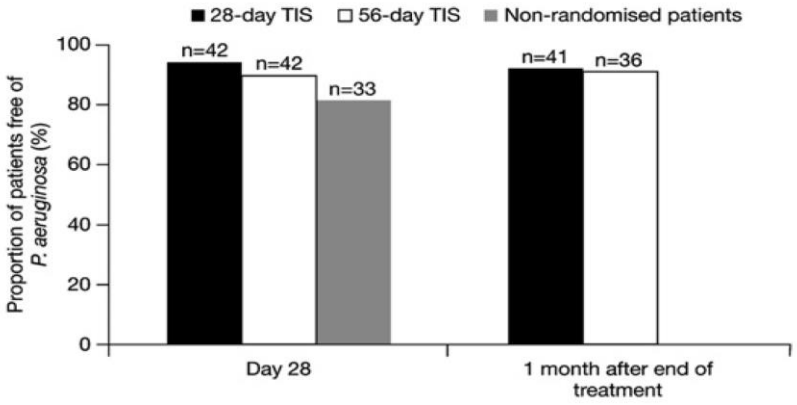
Eradication

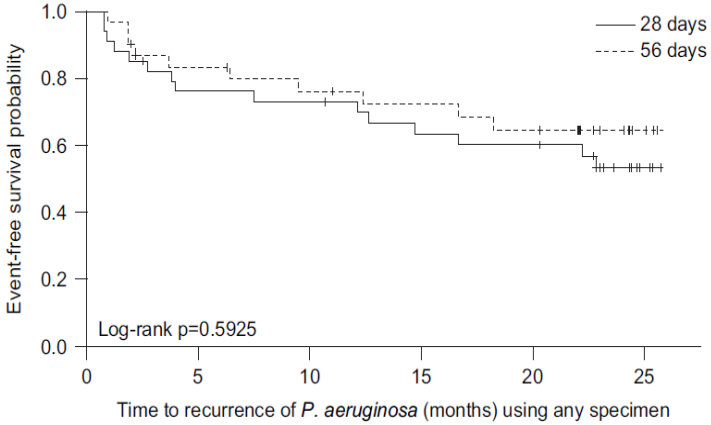
Chronic suppressive therapy

Microbiologic Evolution



Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial





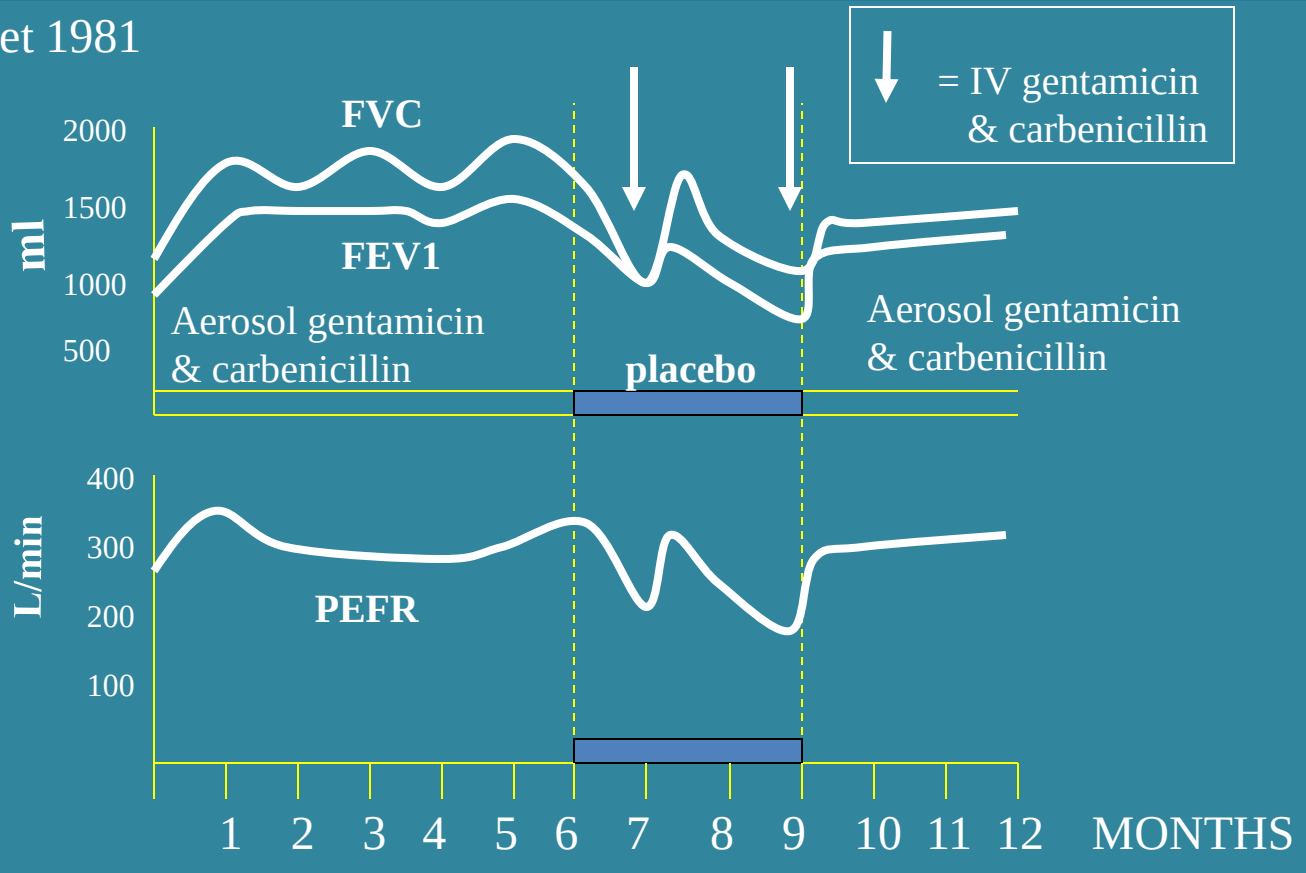
Ratjen F et al. *Thorax*. 2010; 65:286-291.

Chronic Suppressive Therapy

INHALED ANTIBIOTICS

MACROLIDES

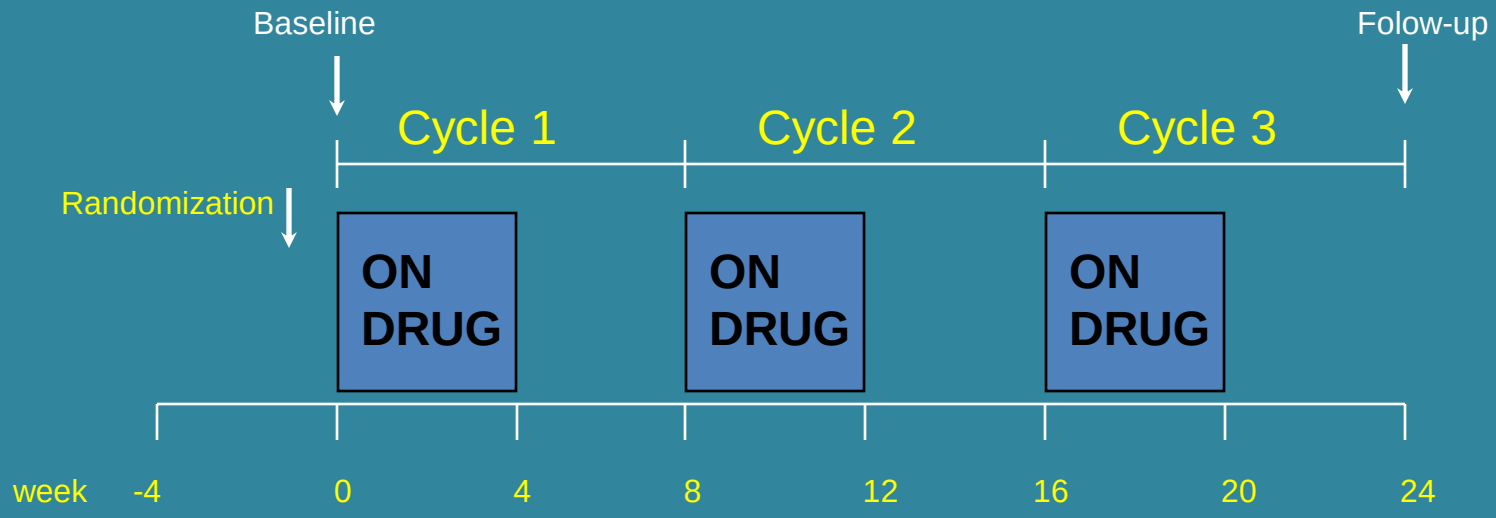
Hodson ME, Lancet 1981



Respiratory function recordings of a patient with CF receiving antibiotics and placebo by aerosol

Study Design TOBI Trial

two parallel studies (002 & 003)

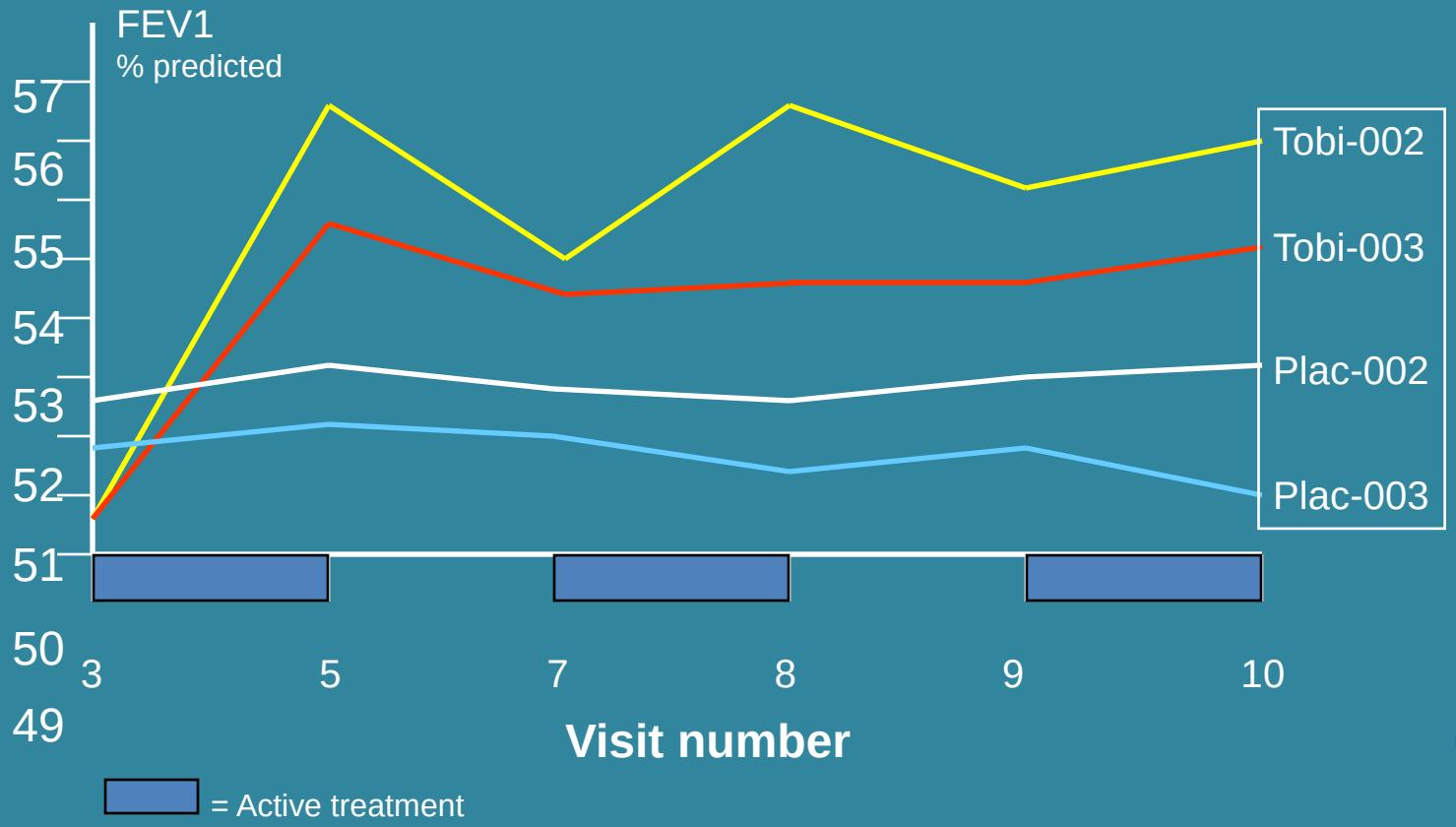


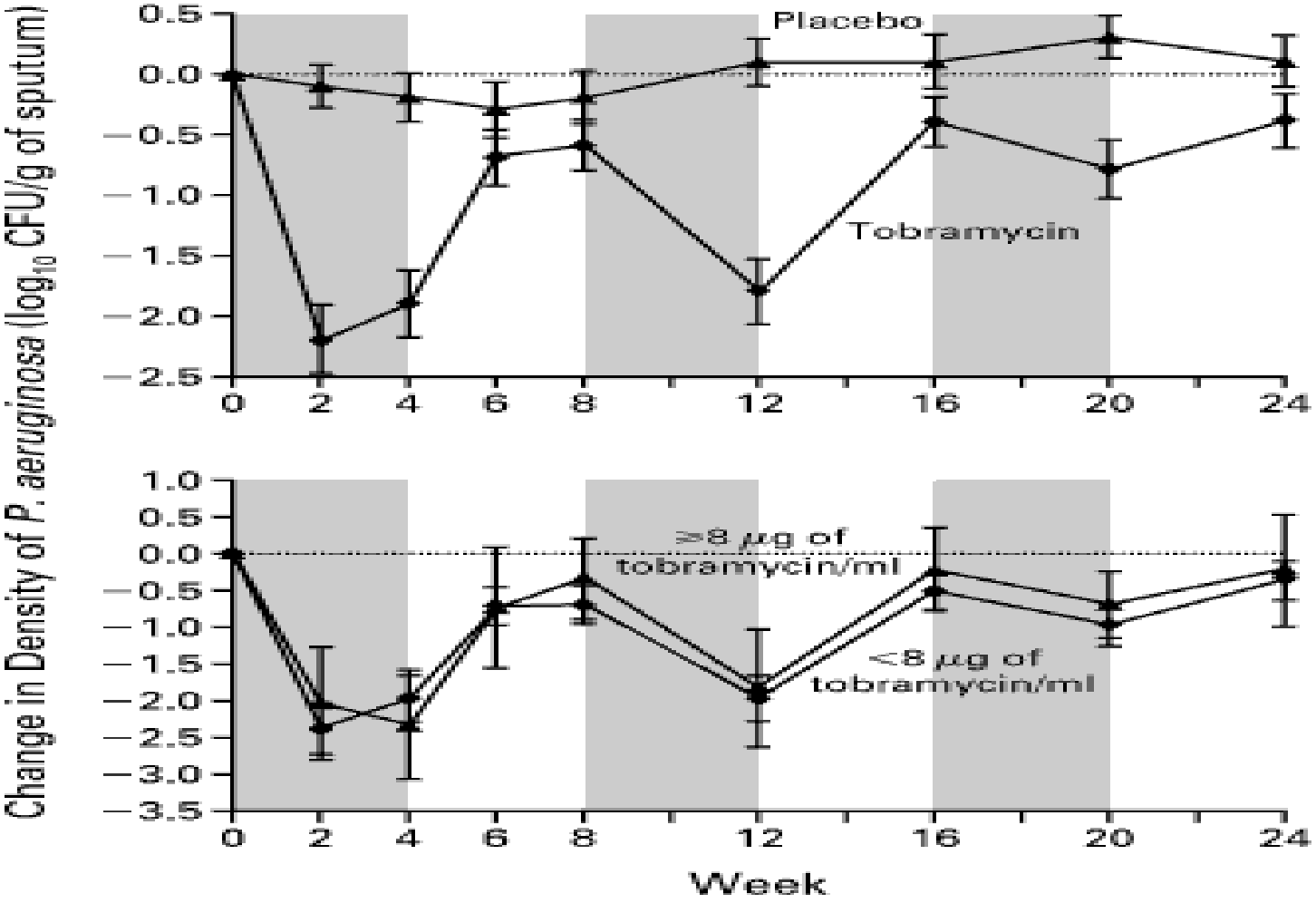
= treatment: 300 mg of tobramycin or quinine in 5 mL of preservative 1/4 NS bid.

Nebulizer = Pari LC plus jet nebulizer

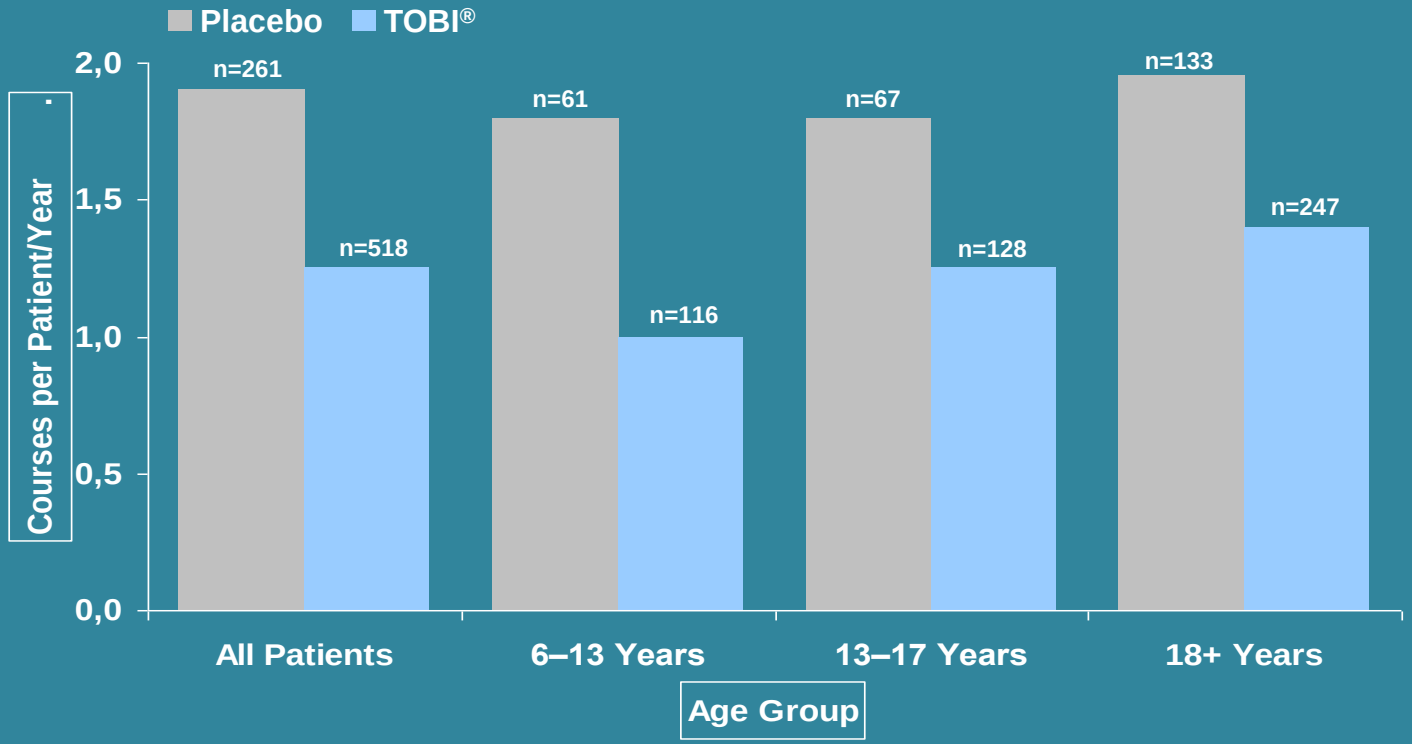
Ramsey NEJM 1999: 340:23-30

Mean FEV1 (% pred.)




Change in Density of P. aeruginosa (log10 CFU/g of sputum)
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
Placebo
Tobramycin
0
2
4
6
8
12
16
20
24
1.0
0.5
0.0
−0.5
−1.0
−1.5
−2.0
−2.5
−3.0
−3.5
≥8 μg of tobramycin/ml
<8 μg of tobramycin/ml
Week

IV anti-pseudomonal antibiotic use



Moss *et al.* Poster and abstract presented at NACF 1999

Antibiotics for Inhalation

Tobramycin solution

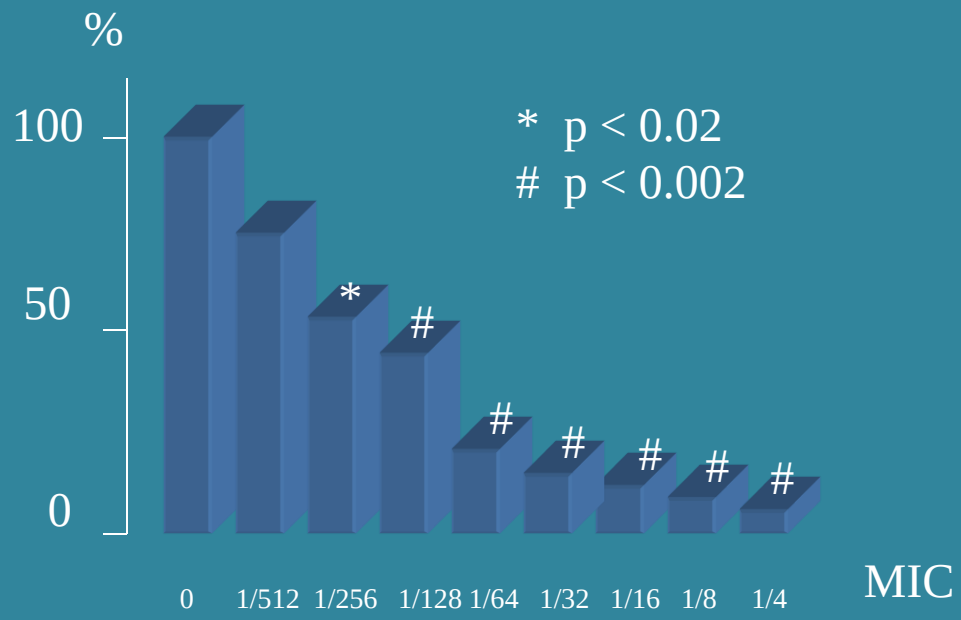
Colomycin solution

Cayston	solution	Aztreonam lysine	B-lactam
TIP	powder	Tobramycin	Aminoglycoside
Colobreathe	powder	Colomycin	
Quinsair	solution	Levofloxacin (Quinsair)	Quinolone

Maar ook:
Ceftazidime, Meropenem en Amikacine……

Macrolides

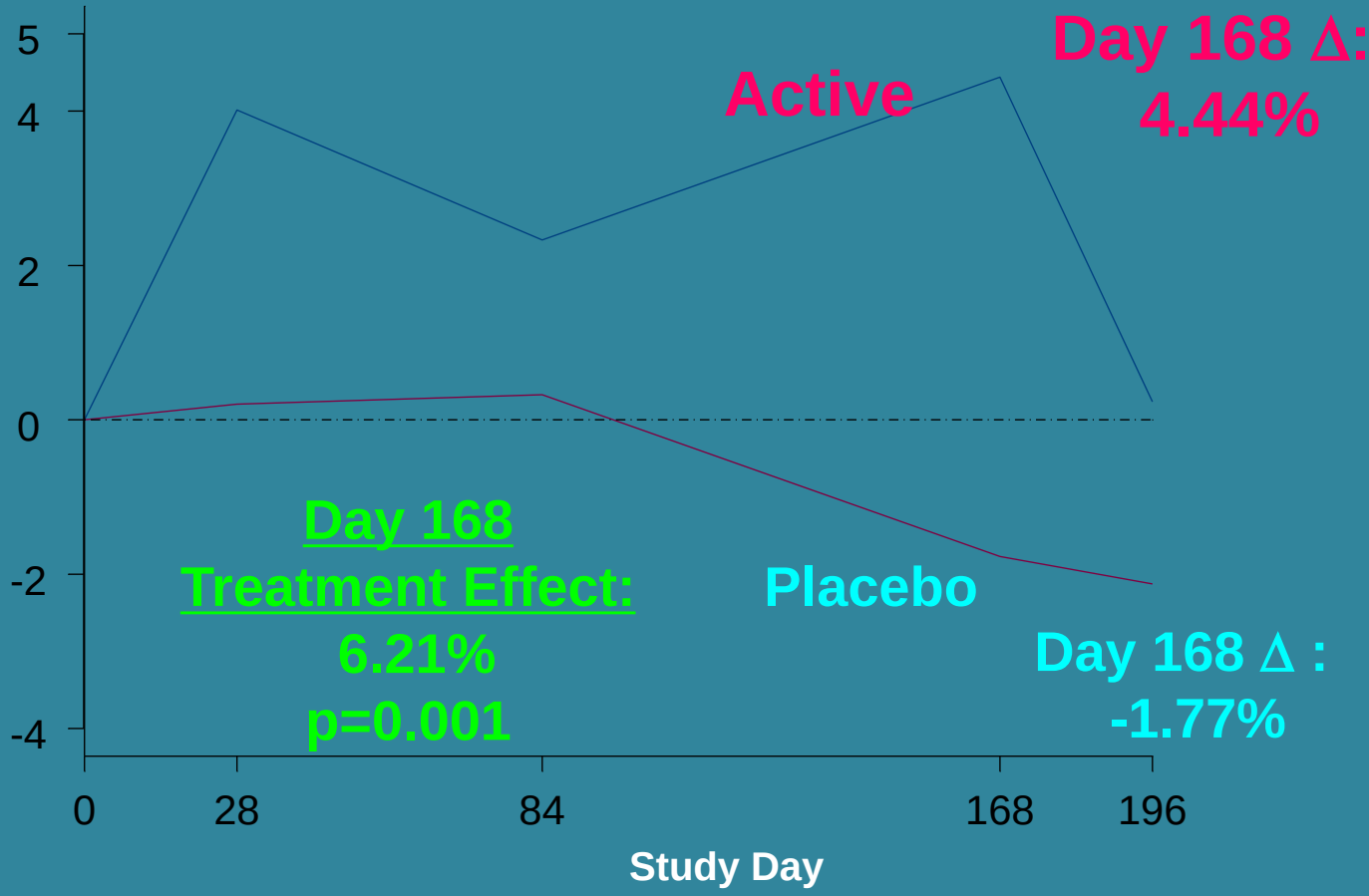
The influence of Azithromycin on Biofilm Formation of Pseudomonas aeruginosa in vitro



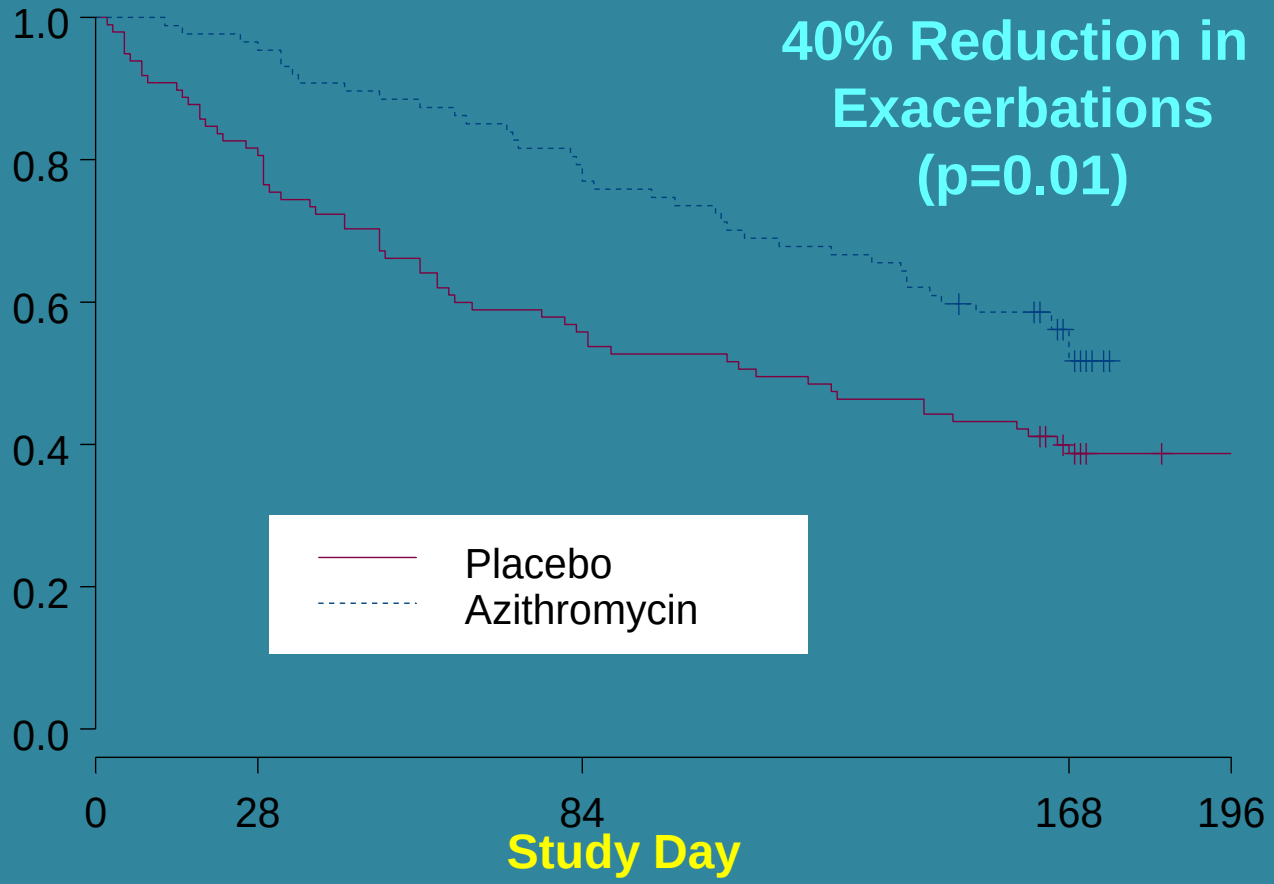
Alginic acid production by P.aeruginosa at subinhibitory concentrations of azithromycin (Data for glycocalyx production are comparable)

Ichimiya Chemotherapy 1996;42:186-91

Relative Change in FEV_1 % Predicted



Proportion of Participants Exacerbation Free



Behandeling van exacerbaties

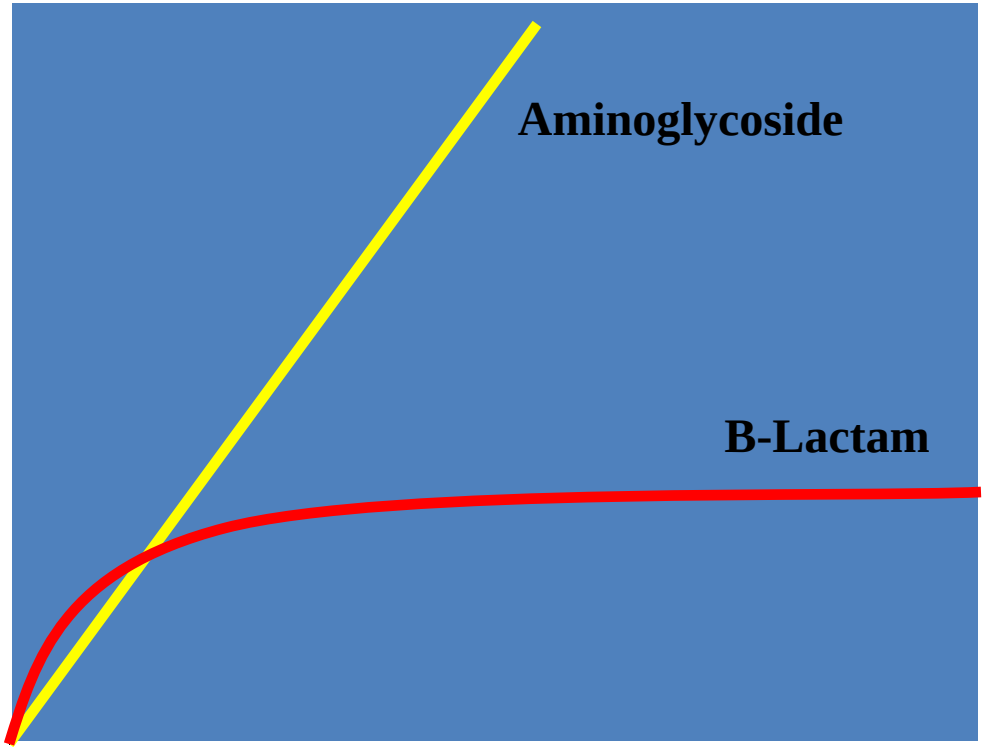
Pseudomonas aeruginosa:

Quinolon
Chlooramphenicol

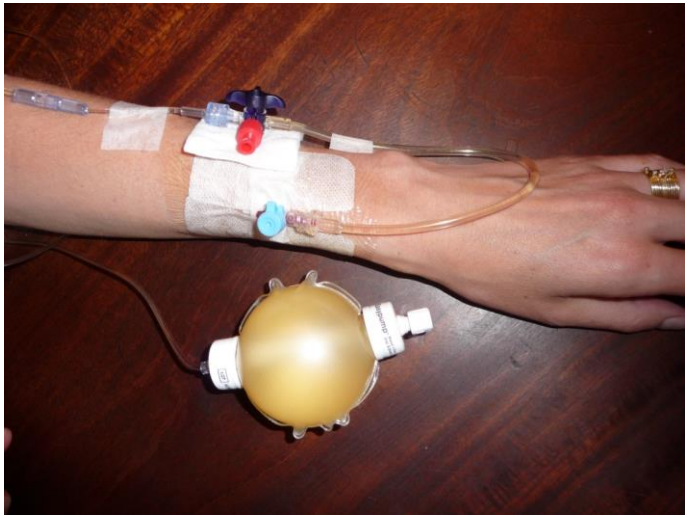
Intraveneus:

Aminoglycoside/Colistine
i.c.m.
Ceftazidime
Aztreonam
Tazocin
Meropenem

Aantal dode bacterien per minuut



CONCENTRATIE



Infuus thuisbehandeling

TELEMEDICINE

Longen

Inhalatie antibiotica/ slikken antibiotica

Mucolytica/sputum mobiliseerders

Luchtwegverwijders

Ontstekingsremmers

KNO

Nasale steroiden
Frequent OK i.v.m. neuspoliepen

Maag Darm Lever Alvleesklier

Pancreasenzymen

Vitamines A, D, E en K

Ursochol

Insuline

Movicolon etc.

Complicaties:

Veel opnames, voornamelijk door toename van de longinfectie

Thuisbehandeling met I.V. antibiotica

Bloedophoesten (Haemoptoe)

Klaplong (pneumothorax)

Rare infecties (Mycobacterie etc.)

Allergisiche reactie op schimmel (ABPA)

Darmverstopping

Diabetes

Osteoporose

Etc, etc.