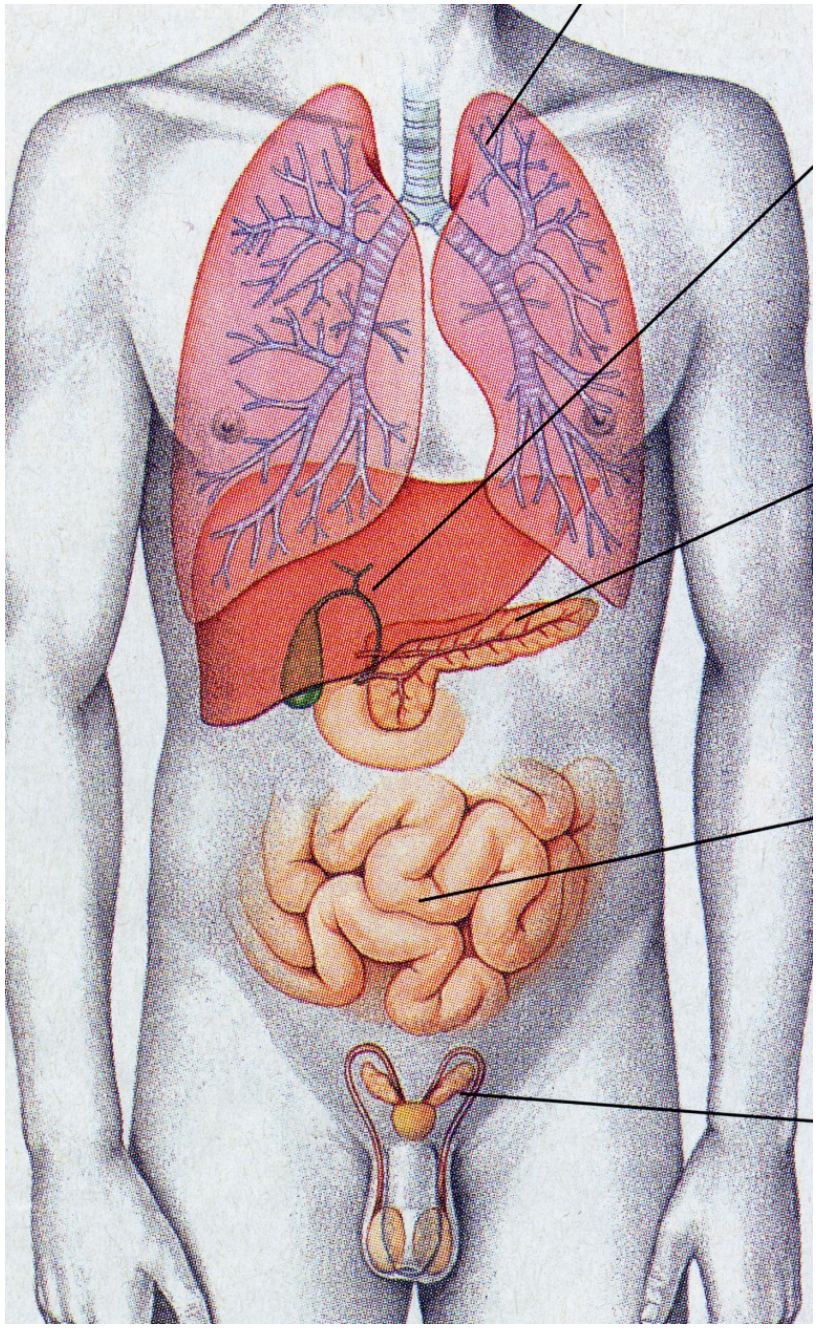


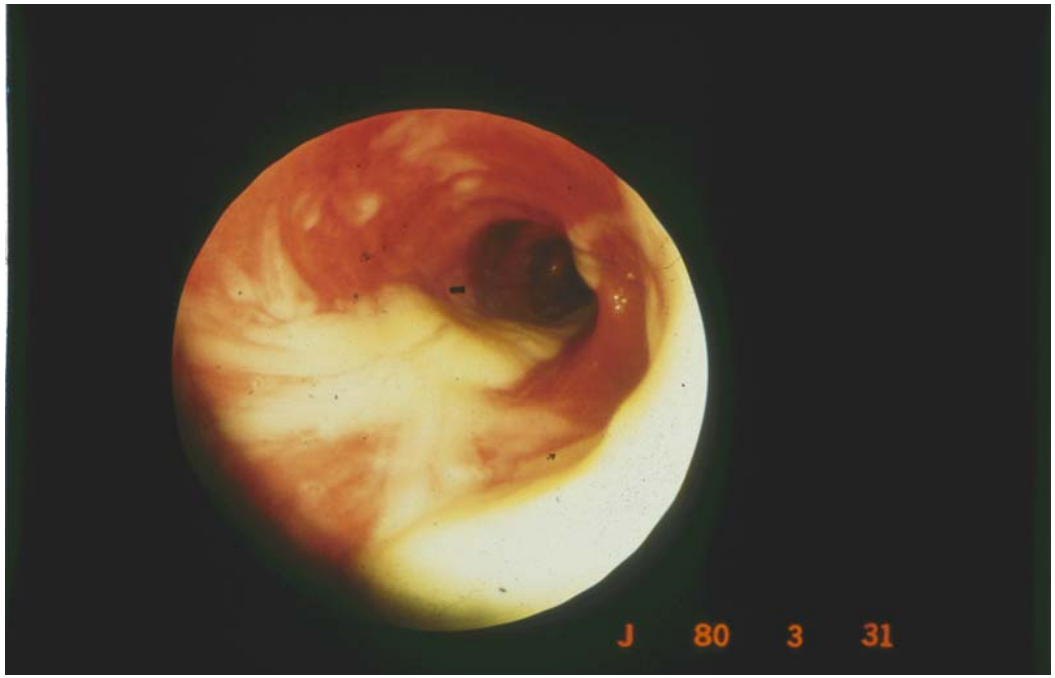
Mukoviszidose

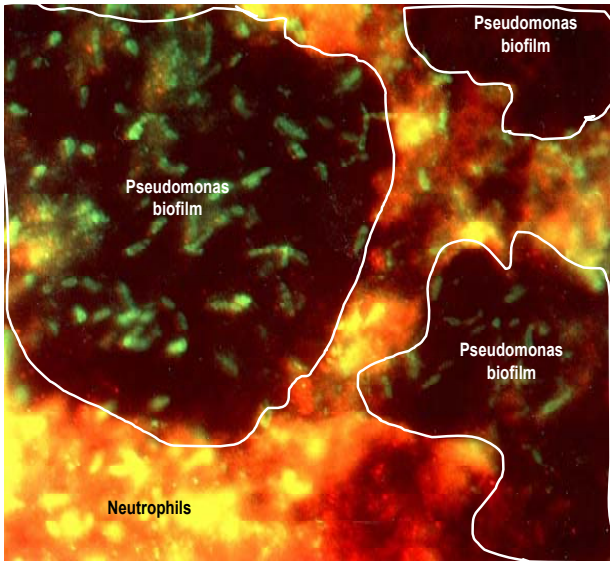
Lungeninfektionen: Pathophysiologie und Therapie

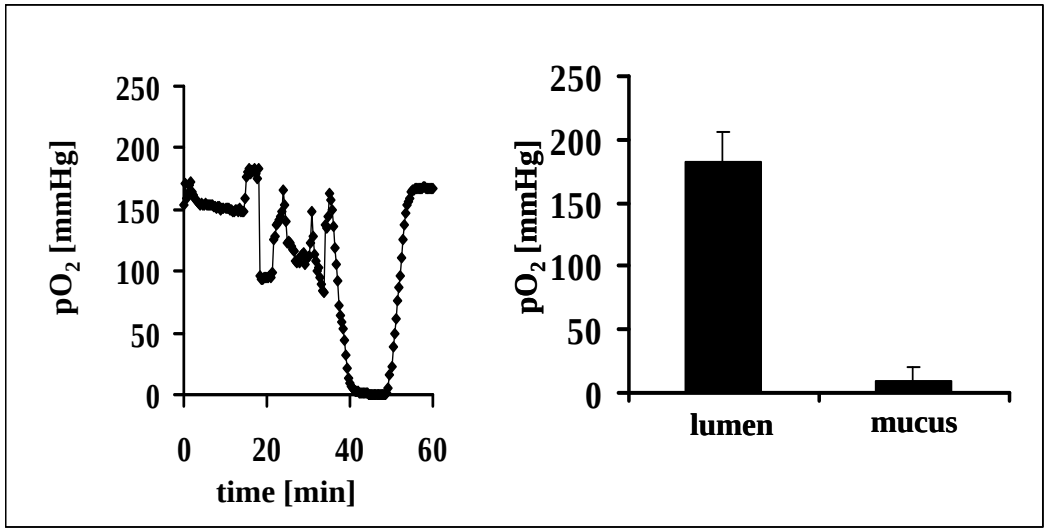
Gerd Döring, Institut für Medizinische Mikrobiologie and Hygiene, Universitätsklinikum Tübingen

Tübingen, 14. December, 2011

Pseudomonas Biofilm Formation





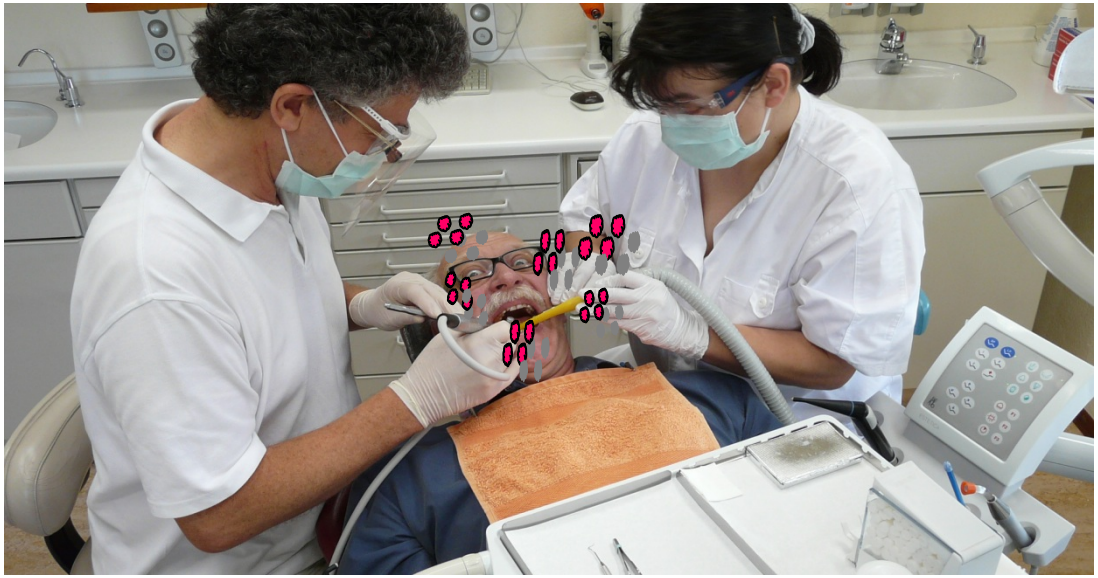


Worlitzsch et al. 2002

Pseudomonas Transmission from the Environment to CF Patients

Sink	CFU	Air	Hand
1	$1.4x10^7$	-	+
2	$2.1x10^8$		+
3	$2.7x10^{10}$	+	
4	$2.4x10^6$	+	
5	$5.4x10^5$	-	
6	$5.2x10^{10}$	+	+
7	$7.0x10^{10}$	+	+
8	$1.0x10^{10}$		+

Döring et al., 1991



Döring et al., unpublished

Surveillance of *P. aeruginosa* Antimicrobial Resistance

	% Resistant				
		CF Isolates			
	Non-CF[1]	HPA 2003[2]	BLT 2005[3]	Mucoid	Non-Mucoid
Ciprofloxacin	20.2%	29.7%	49.3%	49.3%	49.4%
Azlocillin	-		38.9%	34.2%	43.1%
Aztreonam	-		36.4 %	25.3%	46.6%
Gentamicin	22.9%	47%	35.5%	25.6%	44.2%
Meropenem	10.8%		31.6%	24.5%	38%
Imipenem	19%		31.5%	29.6%	33.3%
Ticarcillin/clav	-		28.8%	16.3%	41%
Amikacin	16.6%		28.4%	18.4%	37.4%
Ceftazidime	18.4%	39.6%	25.4%	22.3%	28.1%
Pip/Taz	14.5%	31.9% *	23.3%	19.7%	26.4%
Tobramycin	9.6%	10.1%	21.9%	14.4%	28.6%
Colistin	-	3.1%	0.9%	0%	1.7%

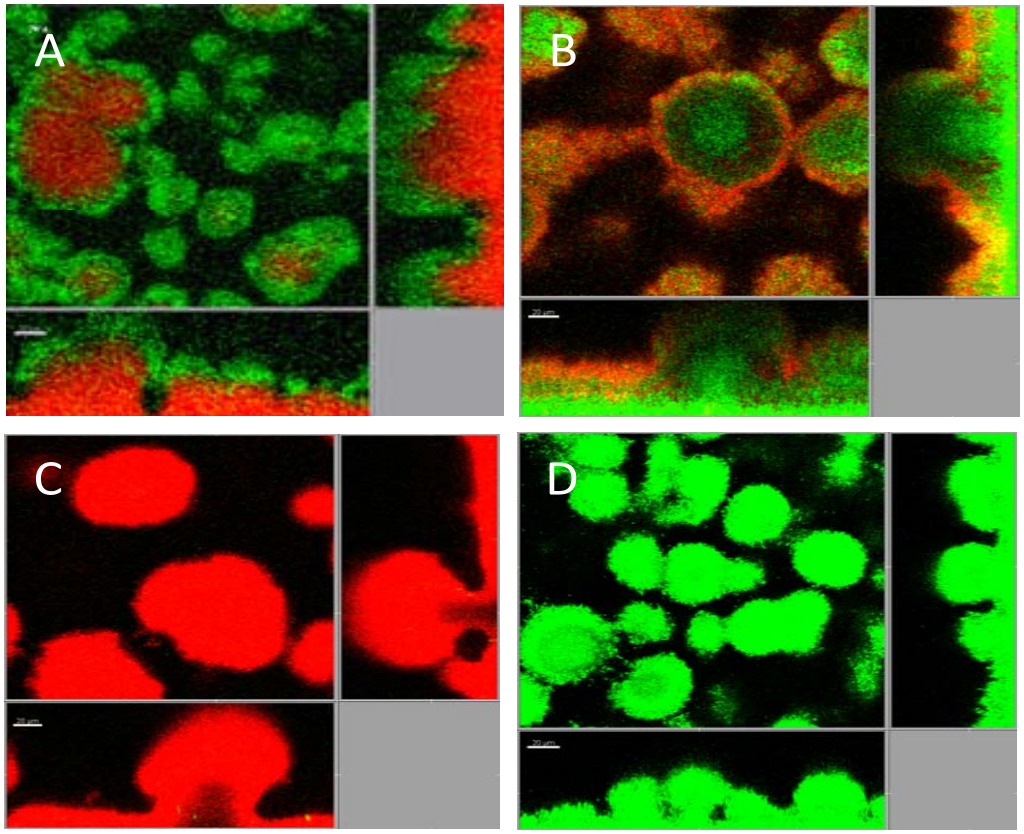
[1]MYSTIC Database [2]Pitt *et al*, Thorax, 2003 [3]Soleimanian *et al*, ICAAC, 2006

Antibiotika-Therapie gegen Pseudomonas-Infektionen bei CF-Patienten

In vitro

Colistin

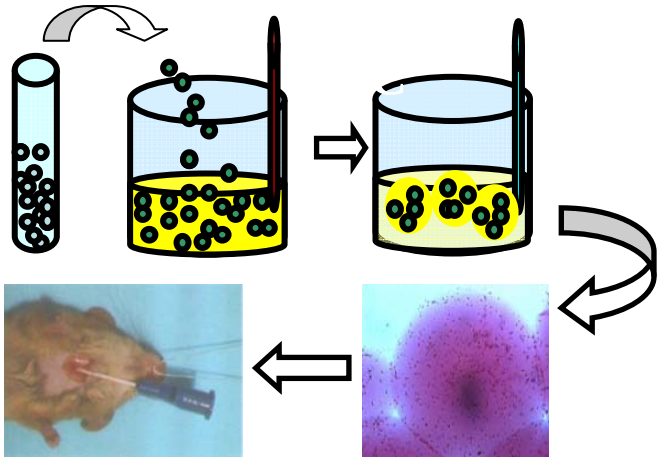
Tobramycin



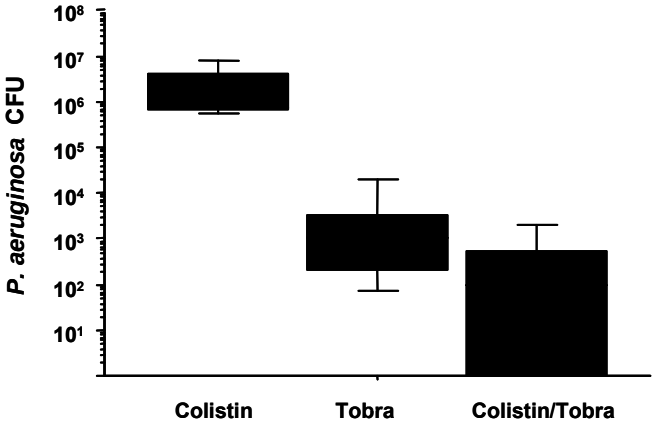
Colistin + Tobramycin

Control

Hermann et al. 2010

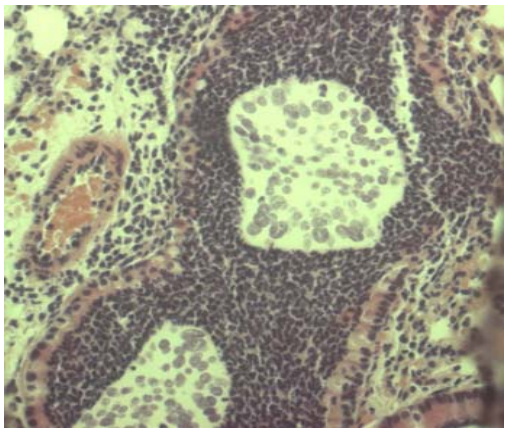


Bragonzi et al., 2005

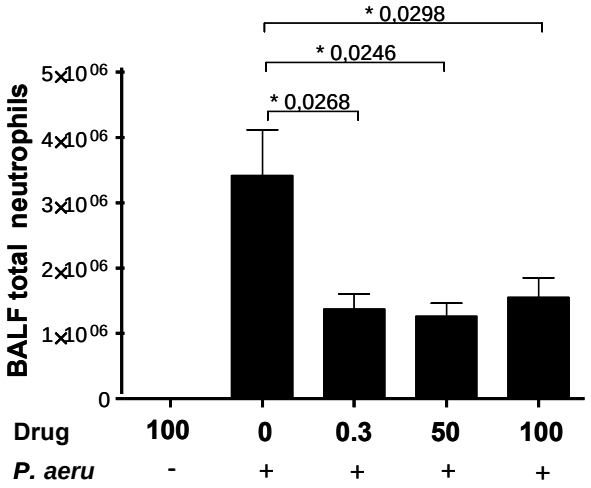


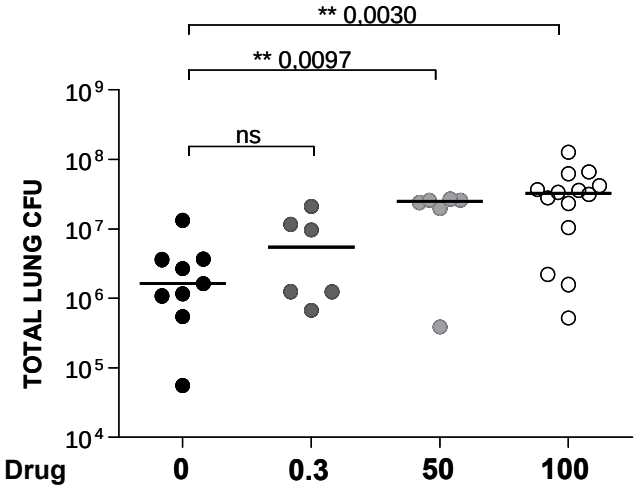
Hermann et al., 2010

Anti-entzündliche Therapie



Bragonzi et al., 2005

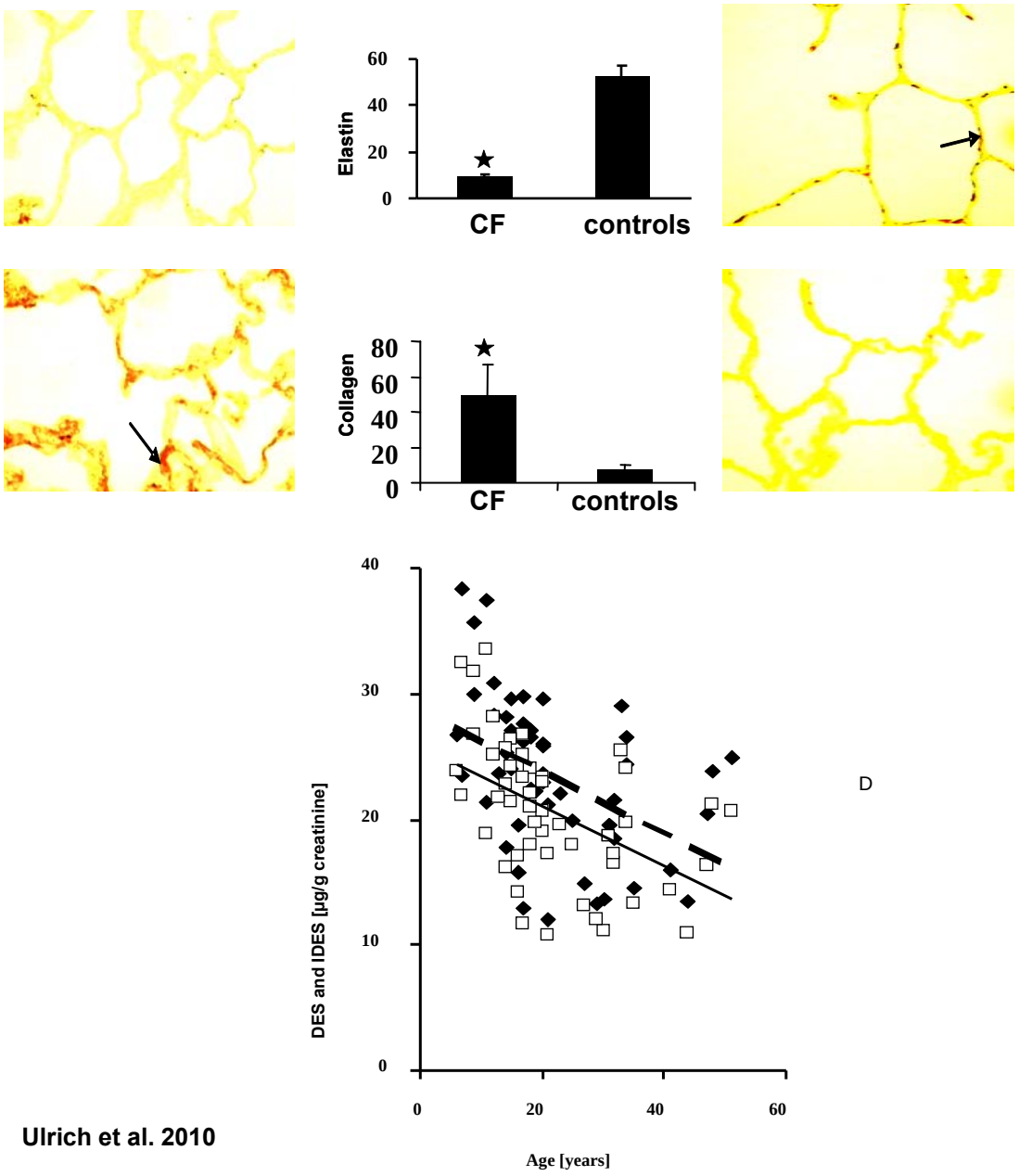




Drug (mg/kg)	% of infected mice blood	spleen	p
0	16	0	
0.3	67	16	0.1
50	50	50	0.01
100	57	50	0.005

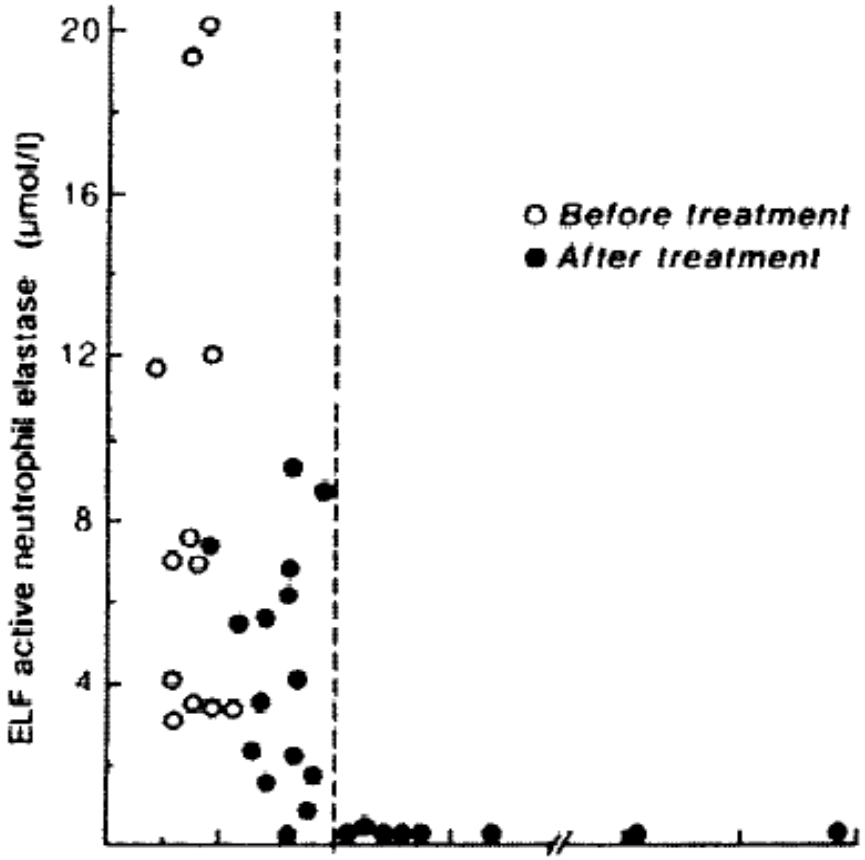
Döring et al., unpublished

Proteolytic damage and tissue remodeling in CF alveoli

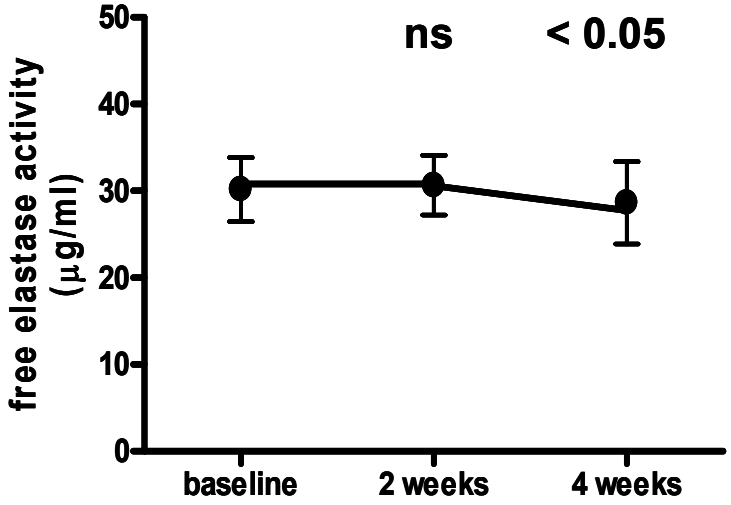


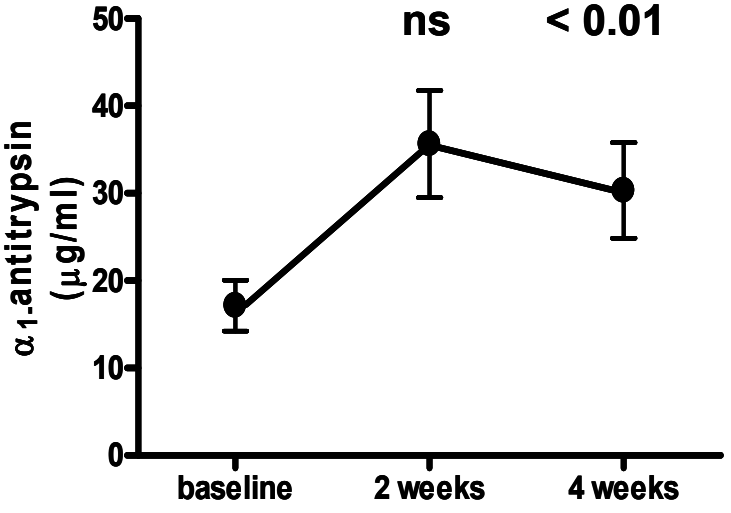
Ulrich et al. 2010

Aerosol α_1-antitrypsin treatment for CF



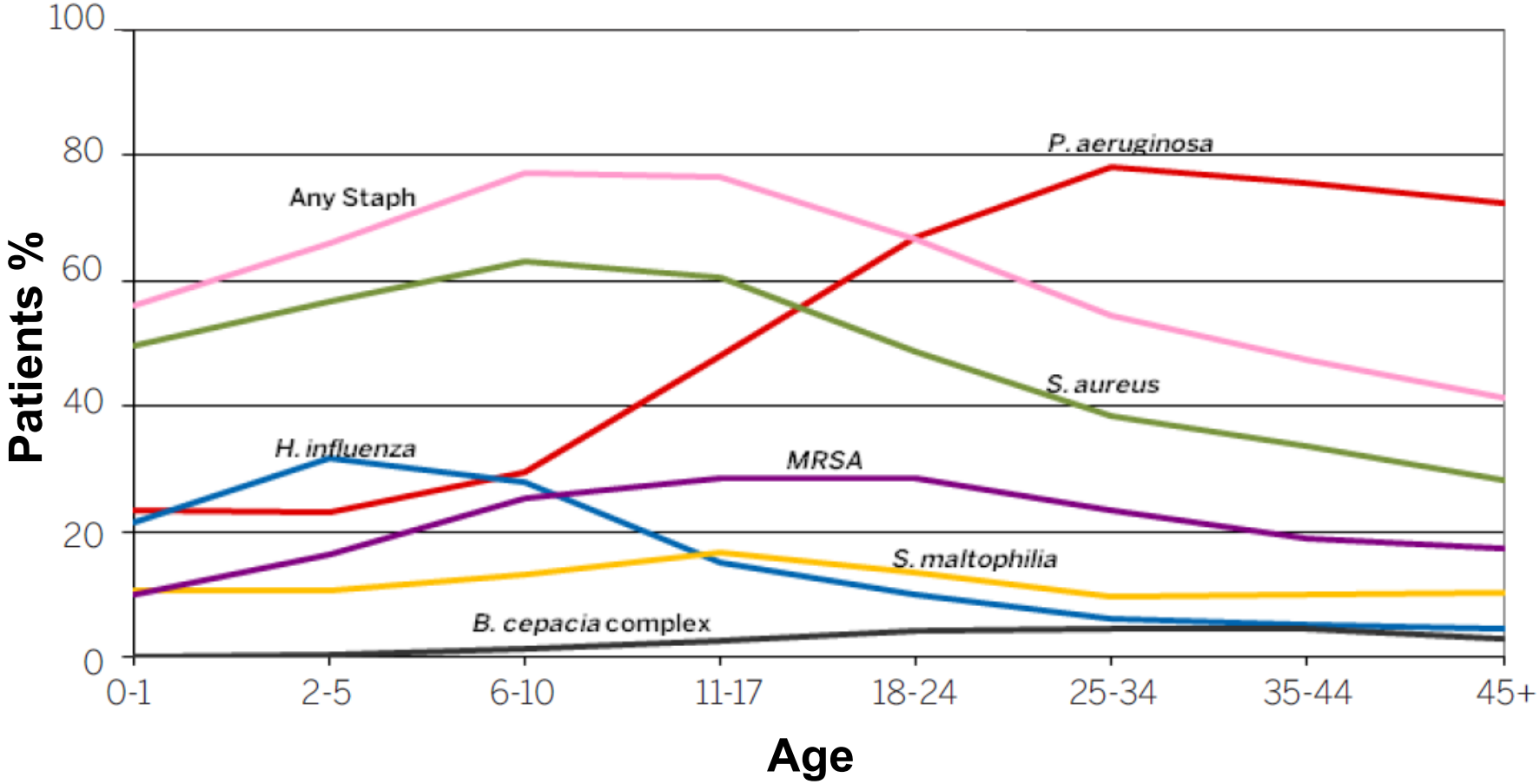
McElvany Lancet 1991; 337:392–394





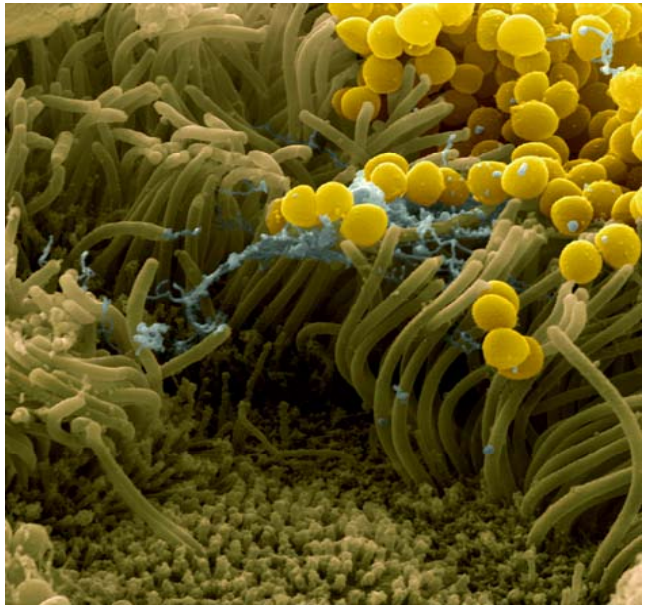
M. Griese, personal information

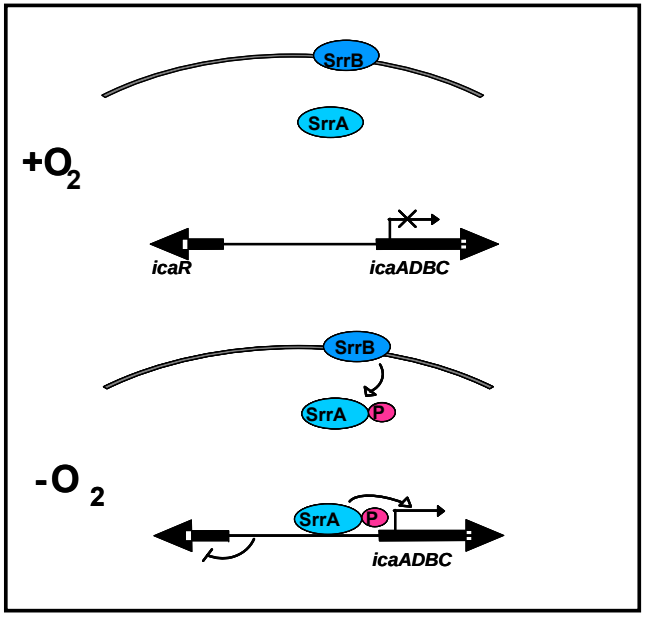
Age specific prevalence of bacterial organisms in CF airways

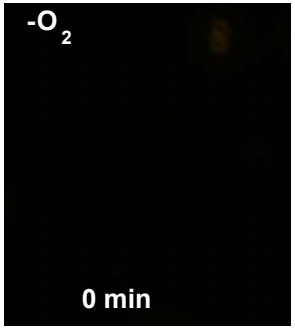


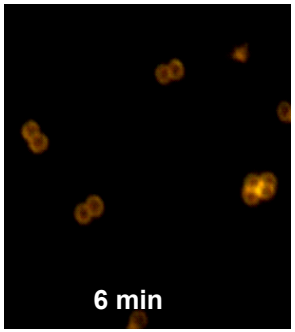
CF Foundation's Patient Registry Annual Data Report 2009

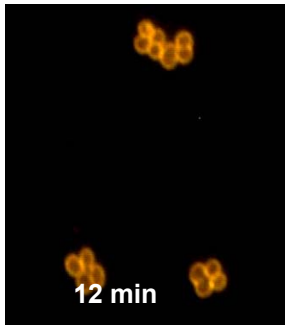
Staphylococcus aureus produces the exopolysaccharide PNAG in the lung of CF patients under anaerobic growth conditions

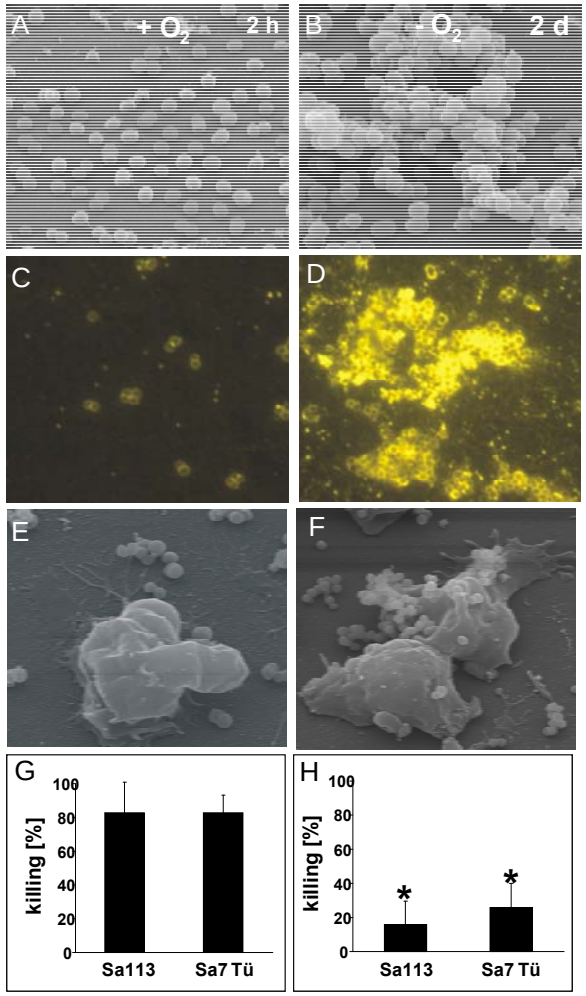












Ulrich et al, Mol Microbiol, 2007

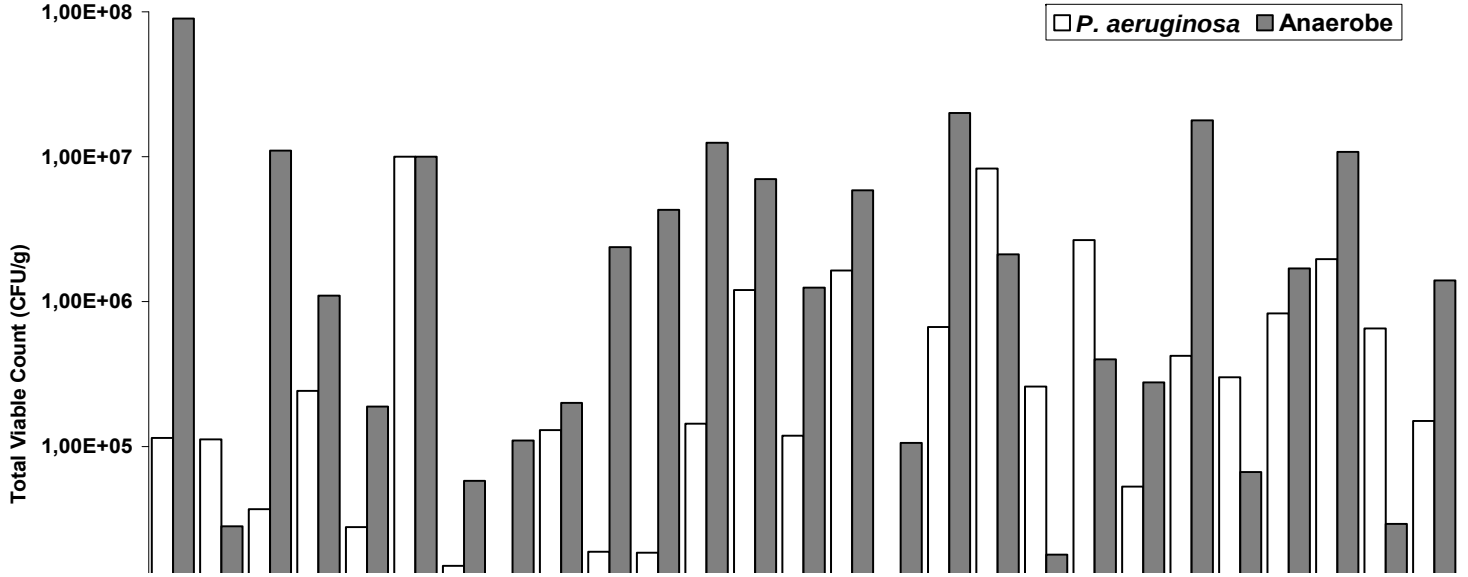
Risk for CF patients to become MRSA-positive

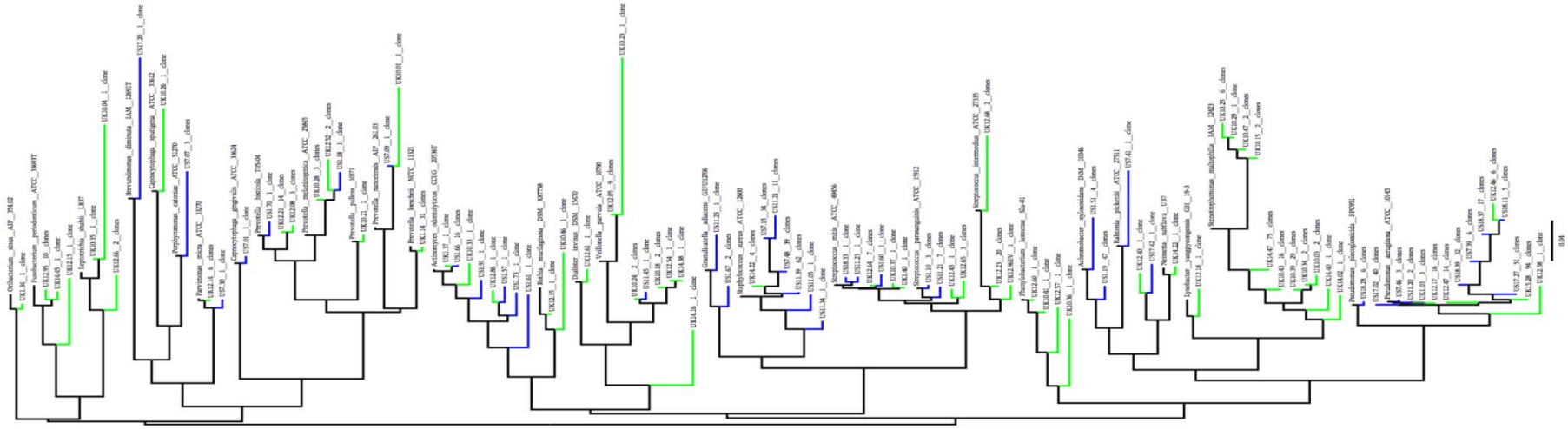
1. **Increased susceptibility for *S. aureus* colonization**
2. **Frequently treated with *S. aureus*-specific antibiotics**
3. **Frequently hospitalized**

Increased prevalence of MRSA among CF patients in USA

- 0.1% in 1995
- 7.0% in 2001
- 18.9% in 2006

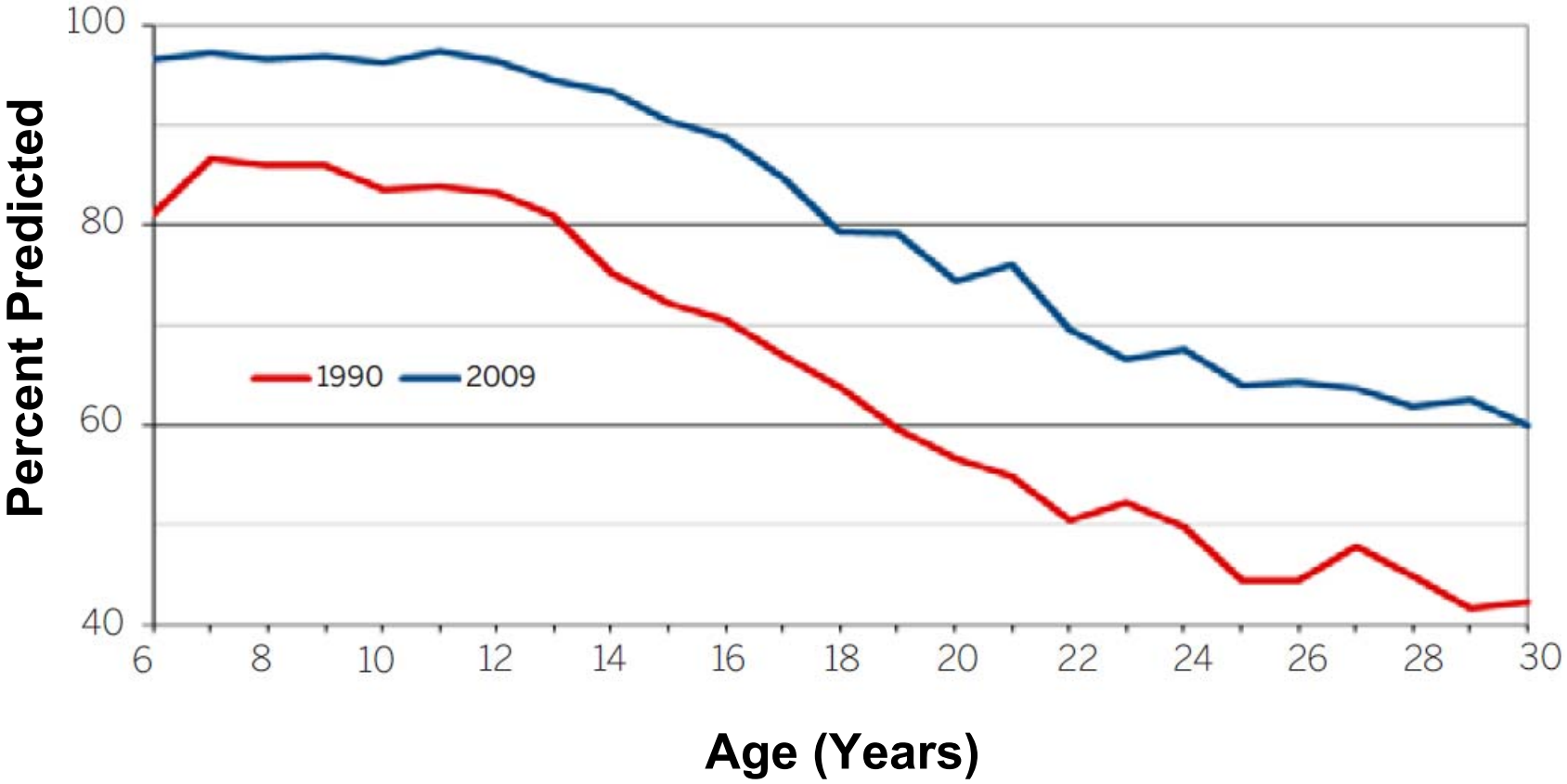
The anaerobes





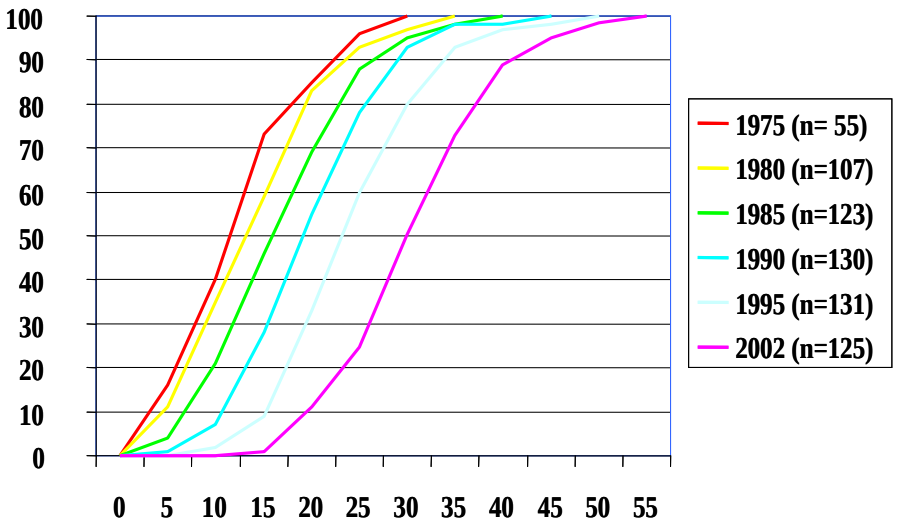
Stressmann et al. 2011

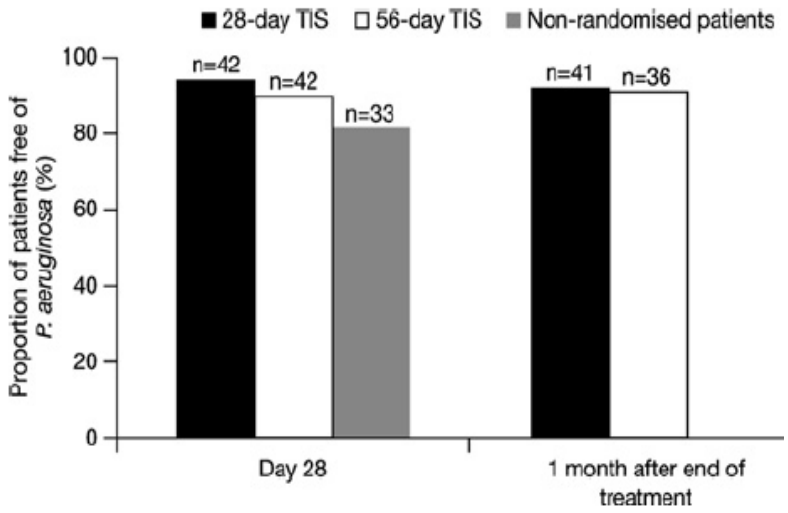
Median FEV_1 Percent Predicted vs. Age, 1990 and 2009



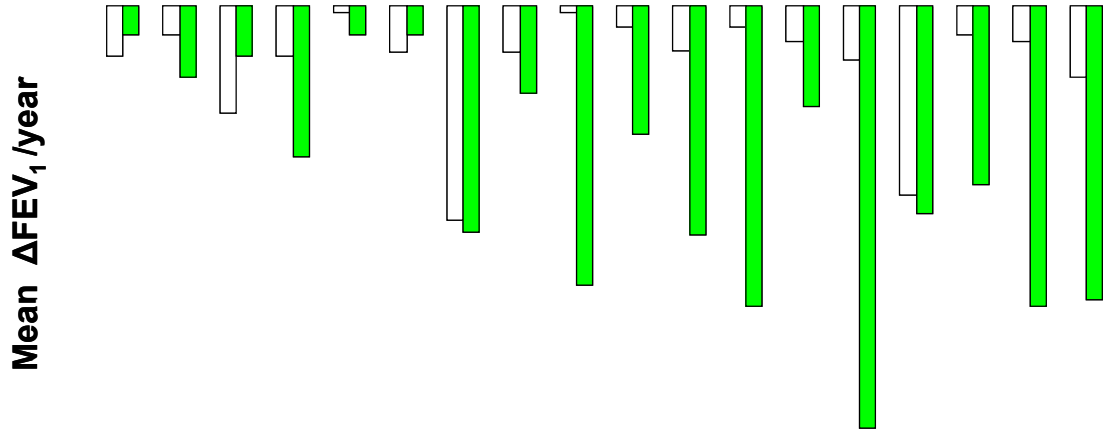
CF Foundation's Patient Registry Annual Data Report 2009

Pseudomonas Antibiotic Therapy





Ratjen et al. 2010

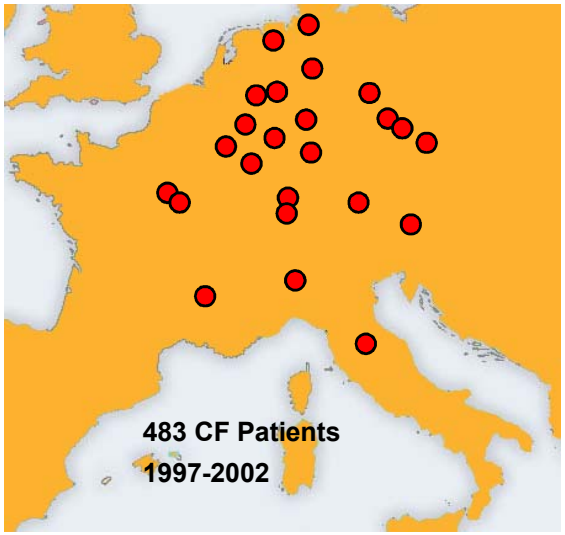


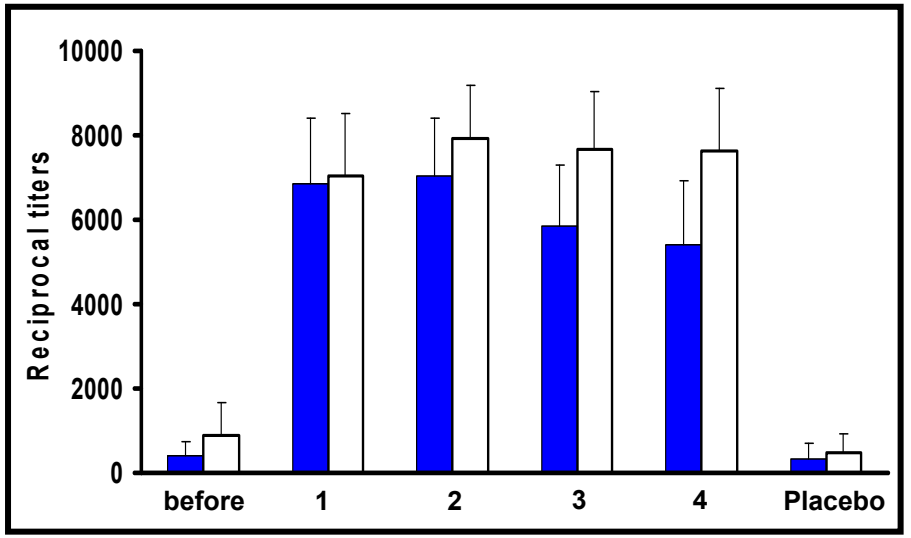
Early eradication ΔFEV_1/yr: -1.65%

Chronic *P. aeruginosa* colonisation ΔFEV_1/yr: -4.74%

Taccetti et al. Eur Respir J 2005; 26:1-4

Vaccination against Pseudomonas

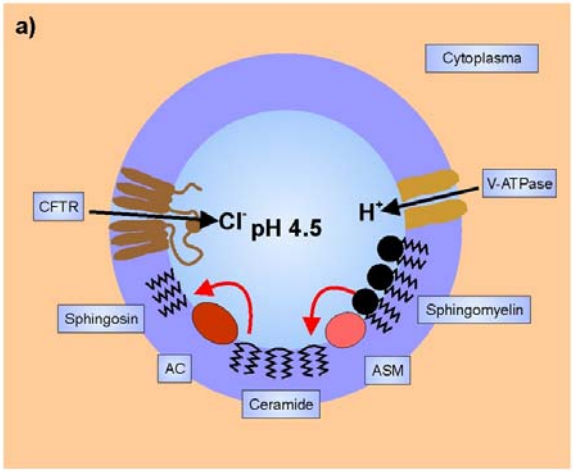


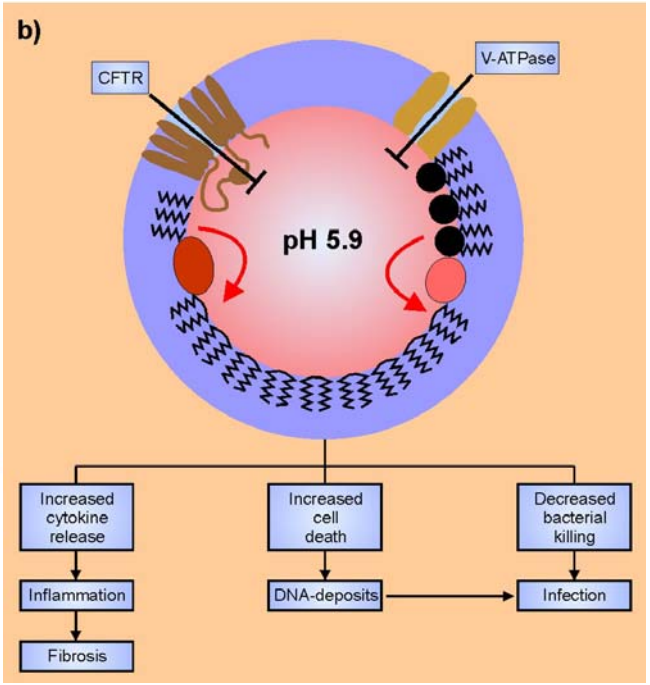


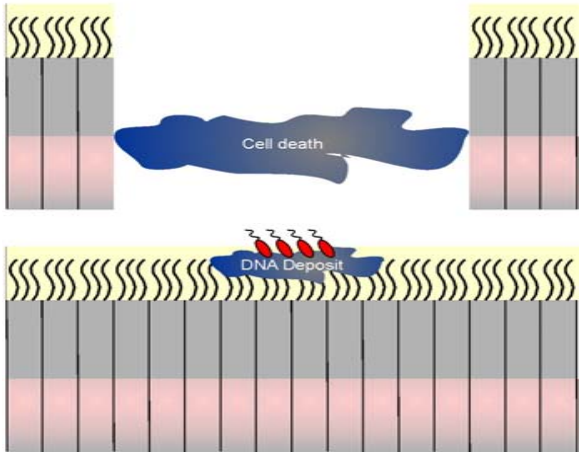
	First Infection		Chronic Infection	
	ITT	PP	ITT	PP
Verum	82	37	26	6
Placebo	105	59	29	12
p	0.05	0.01	0.70	0.15
NNT	11	11	100	32

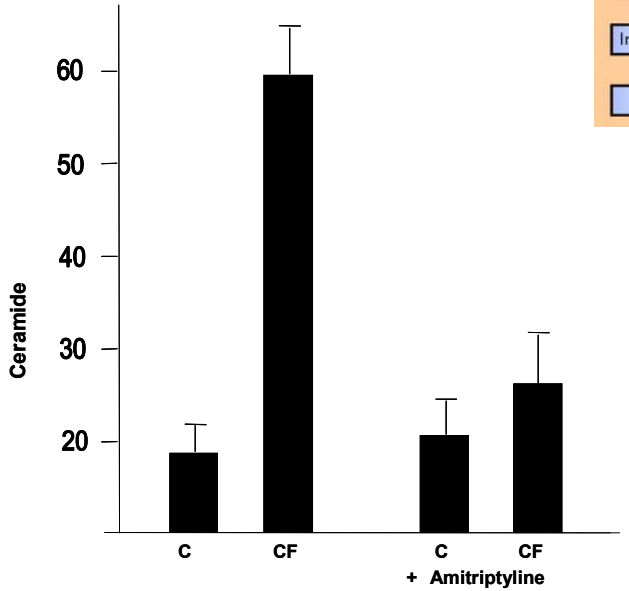
Döring et al., 2007

CF and Ceramide

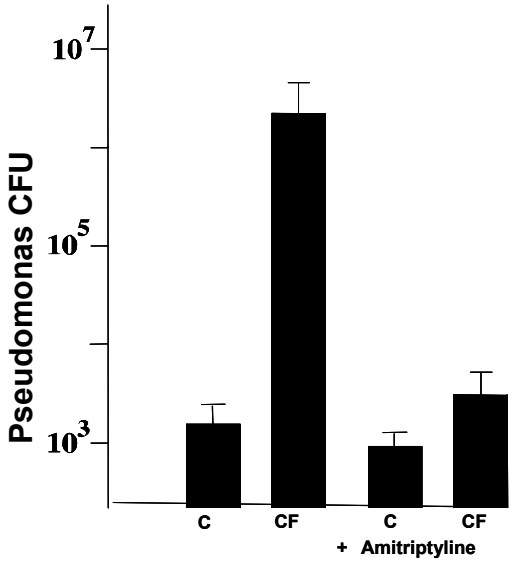




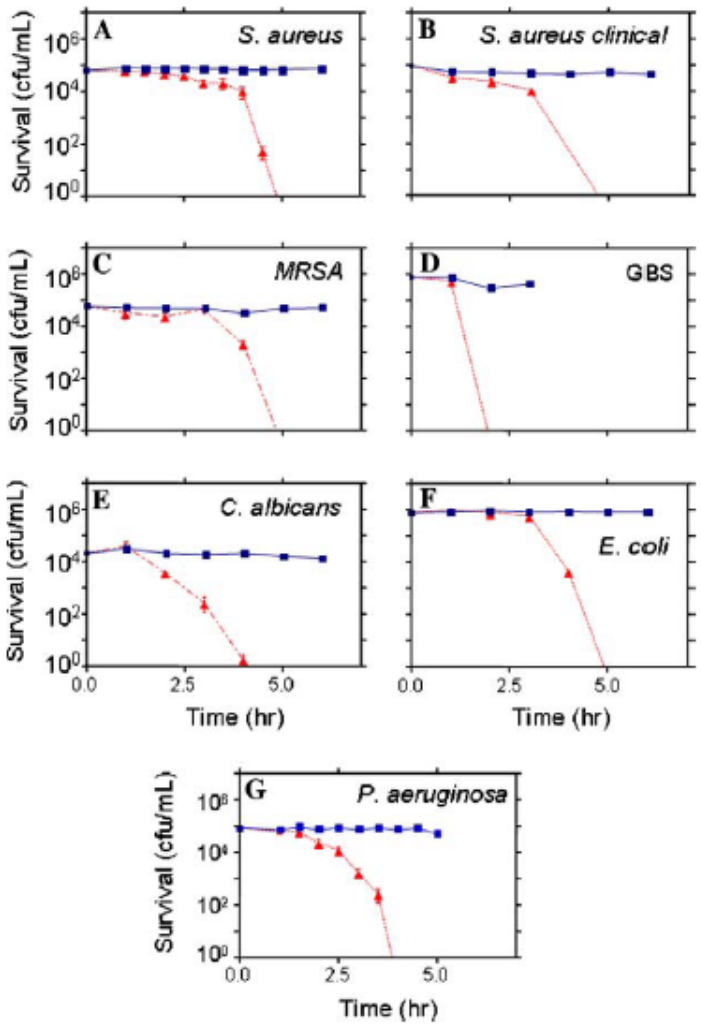




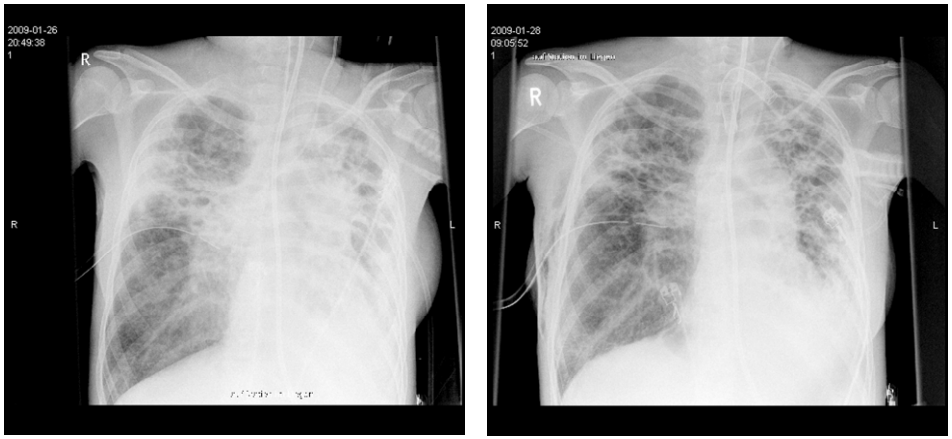
Teichgräber V et al., 2008



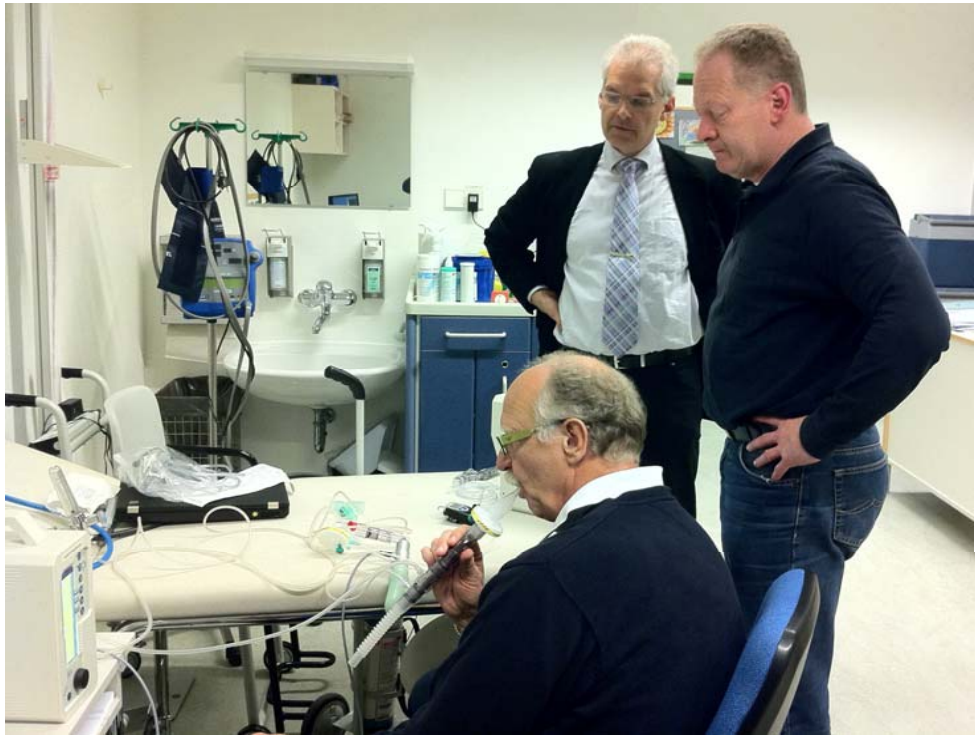
NO ? YES !



Impact of gaseous NO on survival of microbes. Red: 200 ppm NO, blue: air. (Ghaffari A, 2006).



X-ray score of a CF patient who has received pulsed high-dose NO inhalation therapy. Left: before, right: after 2 days of 3 x 30 min of 100 ppm NO. Courtesy of Hubert Wirtz, Leipzig



Zusammenfassung

1. **Die Zahl bakterieller Spezies in infizierten Atemwegen der CF Patienten hat sich erheblich vergrößert und umfasst viele strikte Anaerobier.**
2. **Antimikrobielle Resistenz der CF-spezifischen Pathogene nimmt zu.**
3. **Antibiotische Kombinationstherapie ist eine Alternative zur Monotherapie für chronische *P. aeruginosa* Infektionen.**
4. **Neben *P. aeruginosa* and *S. aureus* sollten möglicherweise auch strikte Anaerobier antibiotisch behandelt werden.**
5. **Hochdosierte NO Therapie könnte Probleme mit resistenten Bakterien lösen.**

Zusammenfassung

1. **Bessere anti-inflammatorischen Medikameente werden benötigt, jedoch stellt diese Therapie ein zweischneidiges Schwert dar.**
2. **Anti-Proteasen Therapie bleibt unbefriedigend.**
3. **Die Antibiotika-Frühtherapie hat die Lungenfunktion und die Lebenserwartung der Patienten erheblich gesteigert.**
4. **Die Vakzine-Entwicklung ist unbefriedigend**