Exacerbation Therapy
What We Know, What We Don't

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M E D I C I N E

CYSTIC FIBROSIS CENTER

Pulmonary Exacerbation

- Increased cough / sputum
- Decreased pulmonary function
- Fatigue
- Hemoptysis
- Weight loss
- Rarely fever

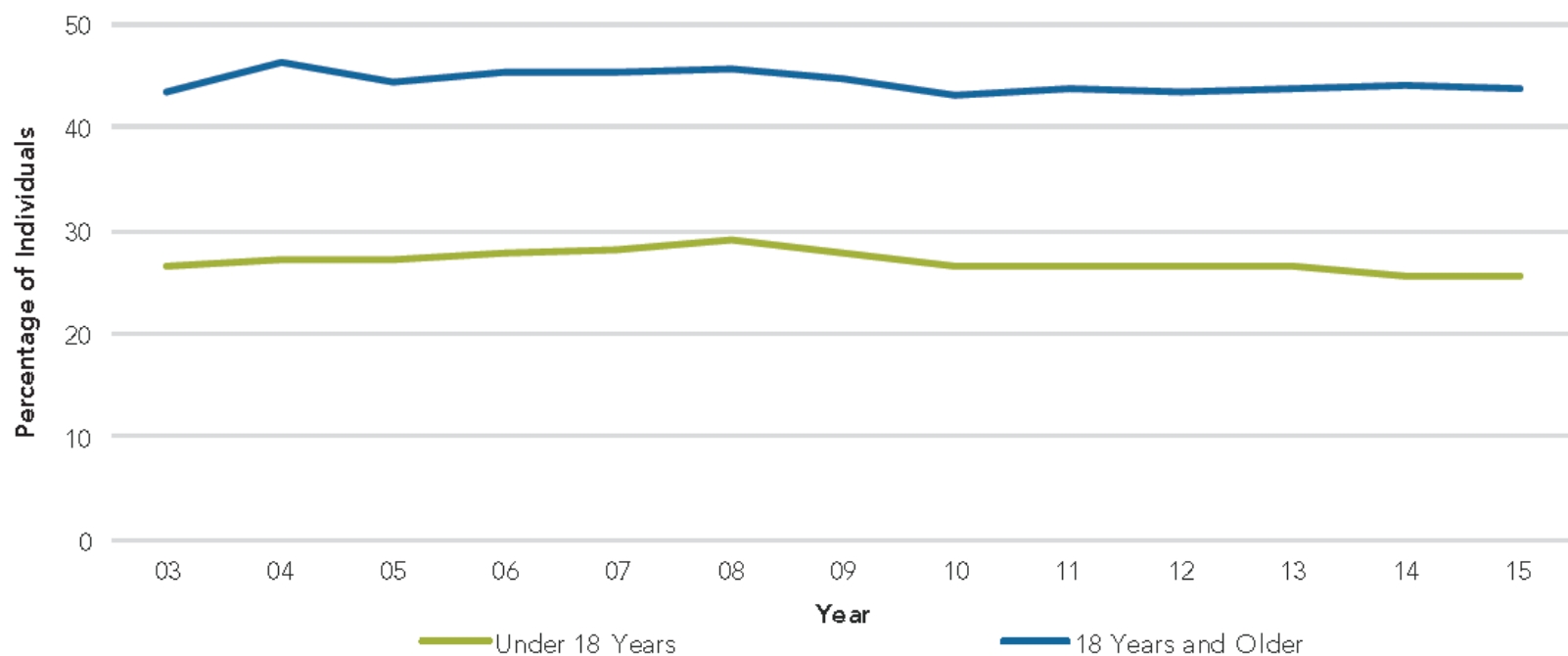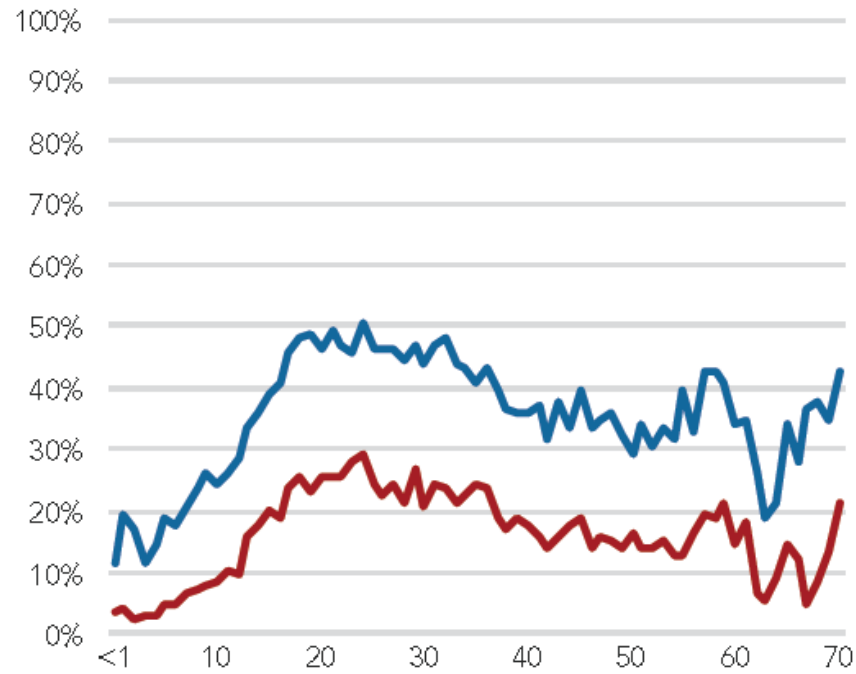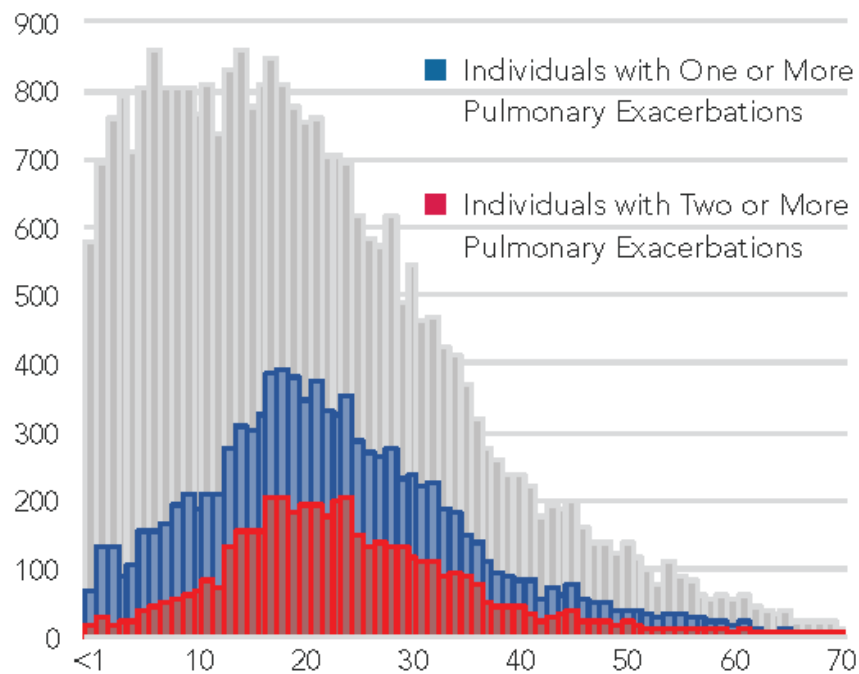# Exacerbation Definition

"I'll know it when I see it"

-Potter Stewart
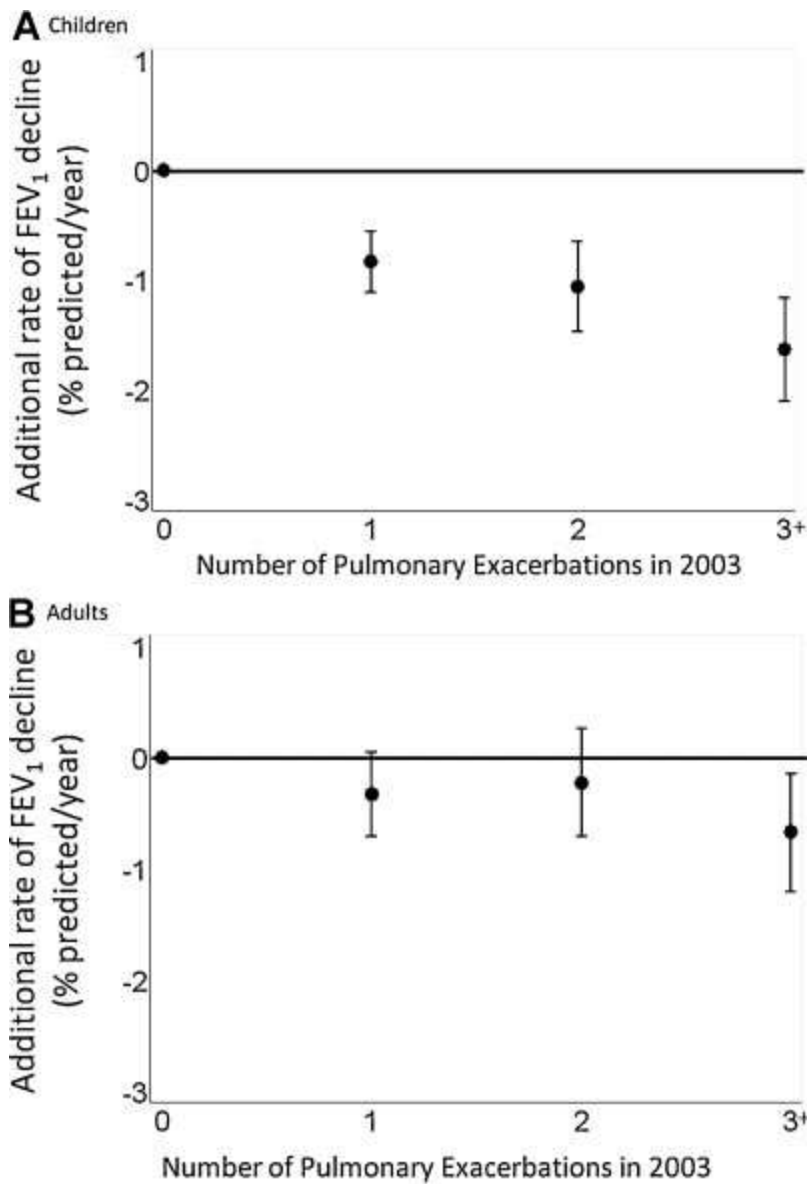
Jacobellis v. Ohio, 1964

Patients Treated with IV Antibiotics for a Pulmonary Exacerbation, 2003–2015

CFF Patient Registry -2015

Pulmonary Exacerbations by Age in Years, 2015

CFF Patient Registry -2015

Effect of Exacerbations on Lung Function

CFF Registry
2003-2006
n=8,400

Failure to Return to Baseline

Variable	OR	95%	CI
Age group (Ref: 7-8 years)			
9-12 years	0.80	0.65	1.00
13-17	0.98	0.80	1.21
18-24	0.83	0.67	1.03
25+	0.89	0.71	1.11
Time since baseline (per week)	1.05	1.04	1.06
Medicaid insurance	1.26	1.14	1.40
Normal BMI	0.68	0.60	0.78
Female gender	1.14	1.03	1.26
Baseline FEV$_1$ (Ref: ≥80% predicted)			
60-79% predicted	0.82	0.70	0.95
40-59% predicted	0.93	0.80	1.08
<40% predicted	1.13	0.94	1.36
Pancreatic insufficiency	1.30	1.01	1.68
P. aeruginosa	1.16	1.04	1.28
B. cepacia complex	1.79	1.31	2.44
MRSA	1.24	1.08	1.42
ABPA	1.31	1.06	1.60
CF Center size (Ref: < 50)			
51-150	0.85	0.71	1.01
≥150	0.75	0.63	0.90

Odds Ratio (95% CI)

>1 = Higher risk of failure

CFF Registry
2003-2006
n=8,479

Sanders *et al. Am J Respir Crit Care Med.* 2010;**182**(5):627-32.
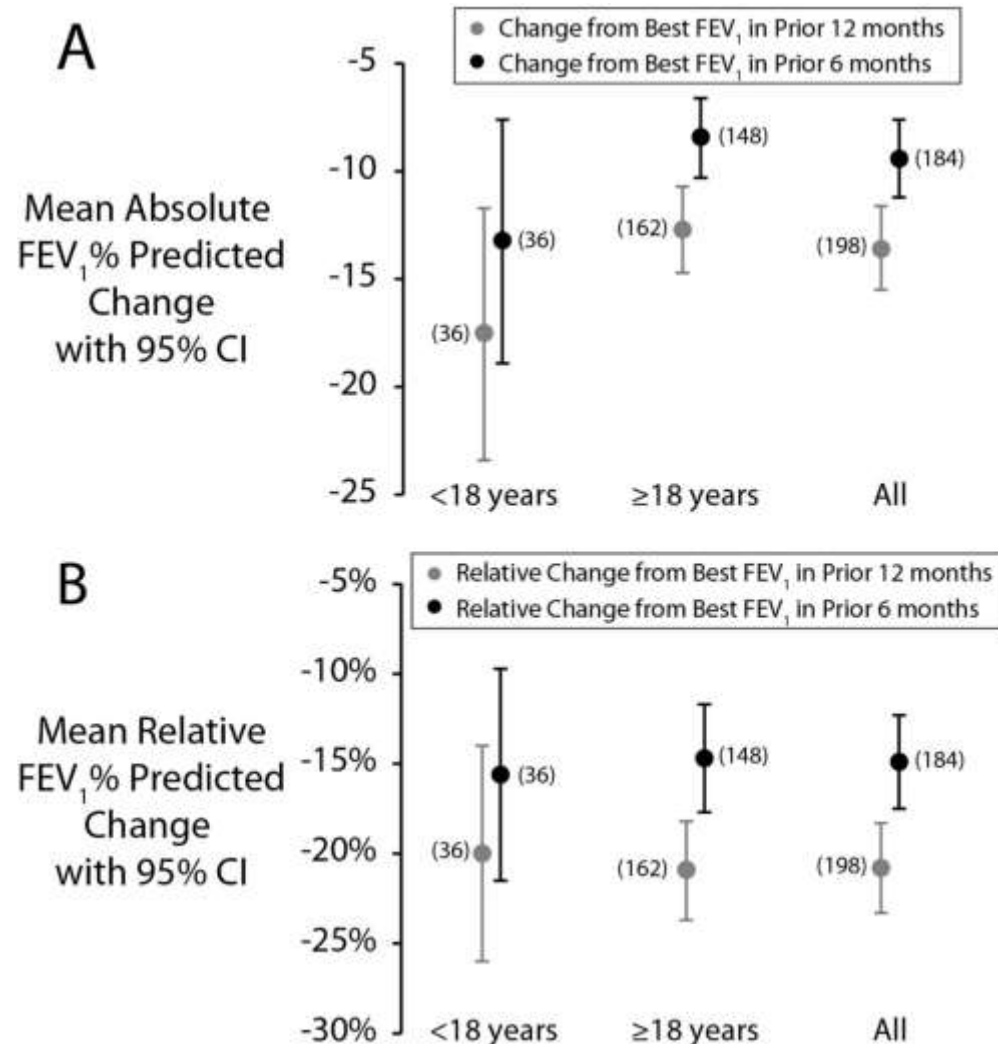
Poor Recovery from Exacerbations is Associated with More Frequent Exacerbations
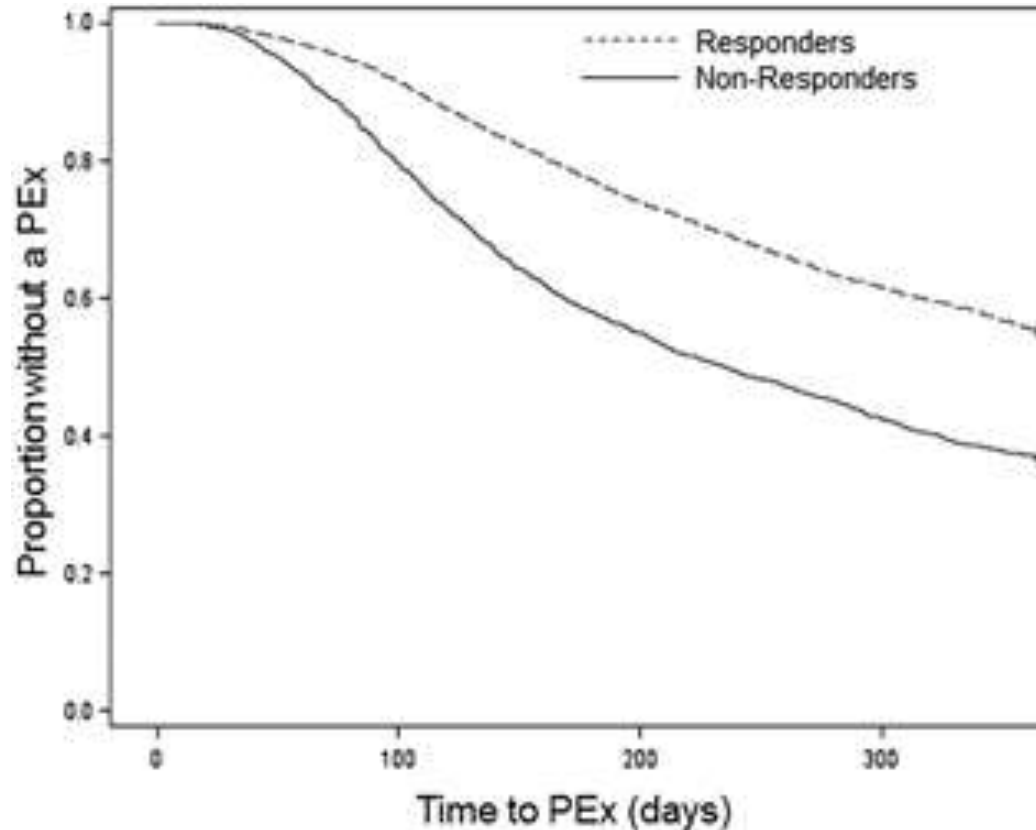
N=13,954 exacerbations
2004-2011

Decision to Treat

N=220
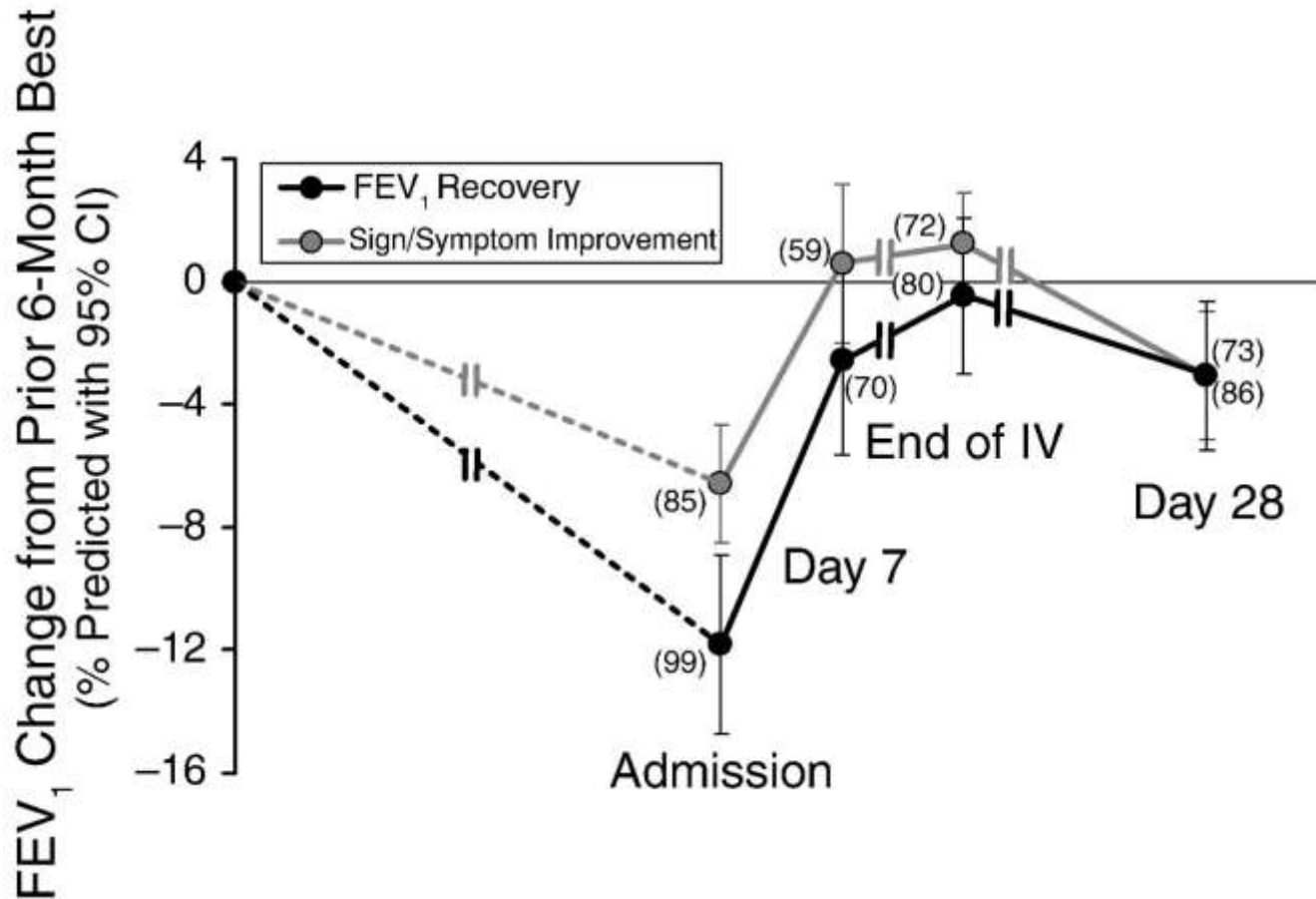≥ 12 years

Saunders *et al. Journal of Cystic Fibrosis* 2017 16, 592-599

Decision to Treat

- Primary Goal
  - Improve Symptoms – 47%
  - Recover Lung Function – 53%
    - Target = Best in last 12 months but 4.5% higher than best in the last 6 months
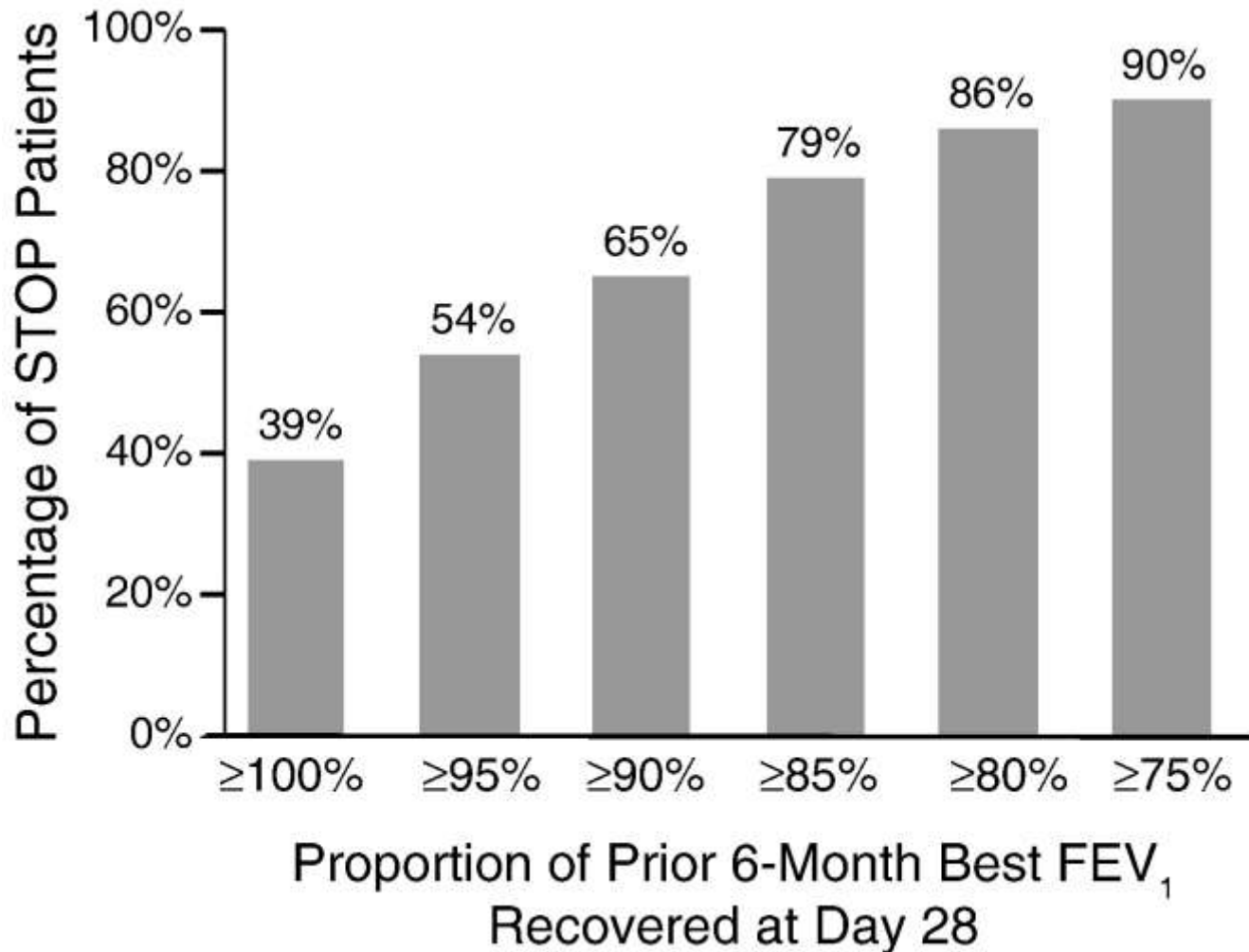- Treatment Protocol with planned duration – 47%

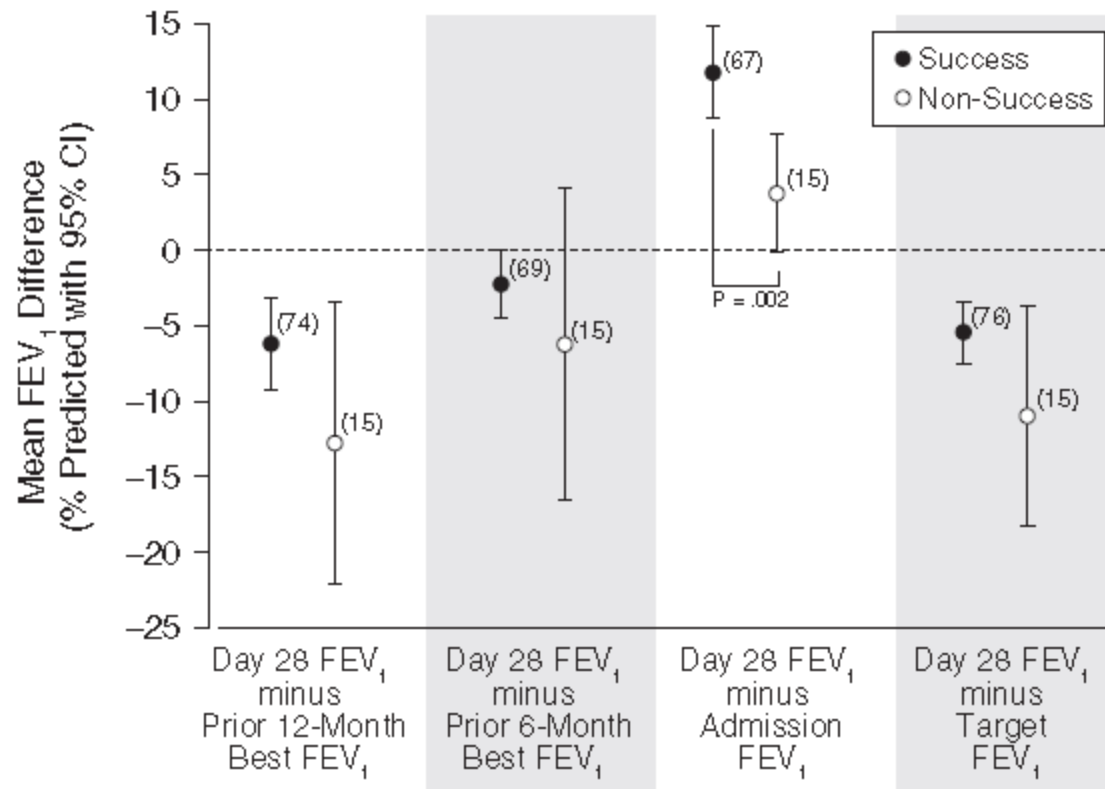# Treatment Success

N=220

≥ 12 years

Treatment Success

N=220

$\geq$ 12 years

West *et al. Journal of Cystic Fibrosis* 2017 16, 600-606

Defining Success

Exacerbation Therapy

- Antibiotics
  - Intravenous
  - Oral
  - Nebulized
- Increased airway clearance
- Treatment of co-morbid conditions
  - Diabetes
  - ABPA
- Disease Education

Cystic Fibrosis Pulmonary Guidelines
Treatment of Pulmonary Exacerbations

Patrick A. Flume[1], Peter J. Mogayzel, Jr.[2], Karen A. Robinson[3], Christopher H. Goss[4], Randall L. Rosenblatt[5], Robert J. Kuhn[6], Bruce C. Marshall[7], and the Clinical Practice Guidelines for Pulmonary Therapies Committee*

Summary of Recommendations

B Recommendation Moderate Benefit	C Recommendation Small Benefit	D Recommendation No Benefit
• Chronic Therapies • Airway clearance	• Once Daily Aminoglycoside Dosing	• Routine synergy testing

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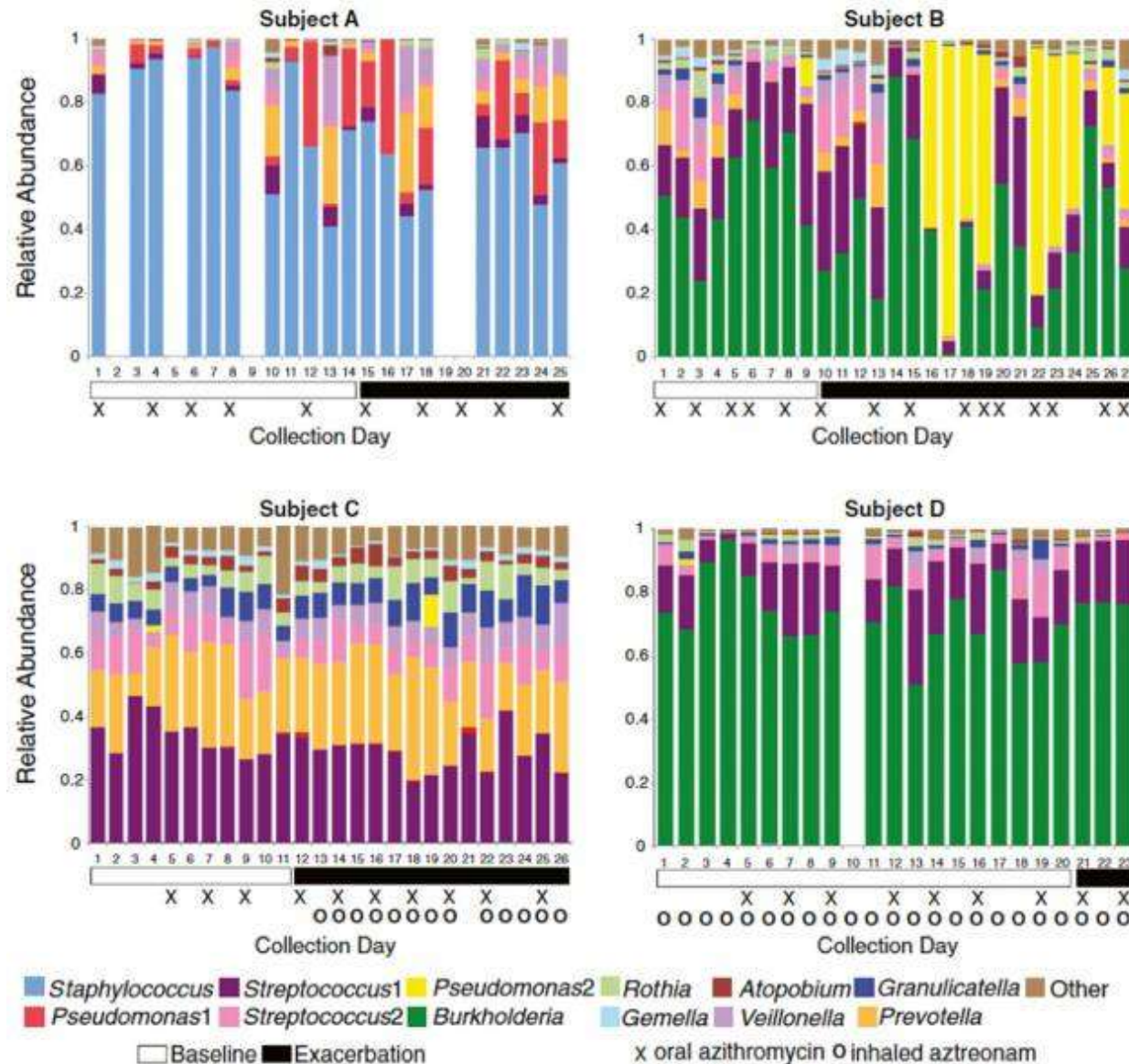
- Optimal approach to therapy is unknown
  - Choice of antibiotics
  - Length of therapy
  - Location of therapy
  - Usefulness of adjunct therapies
    Steroids
    β-agonists

Prevalence of Respiratory Microorganisms by Age Cohort, 2015

CFF Patient Registry - 2015
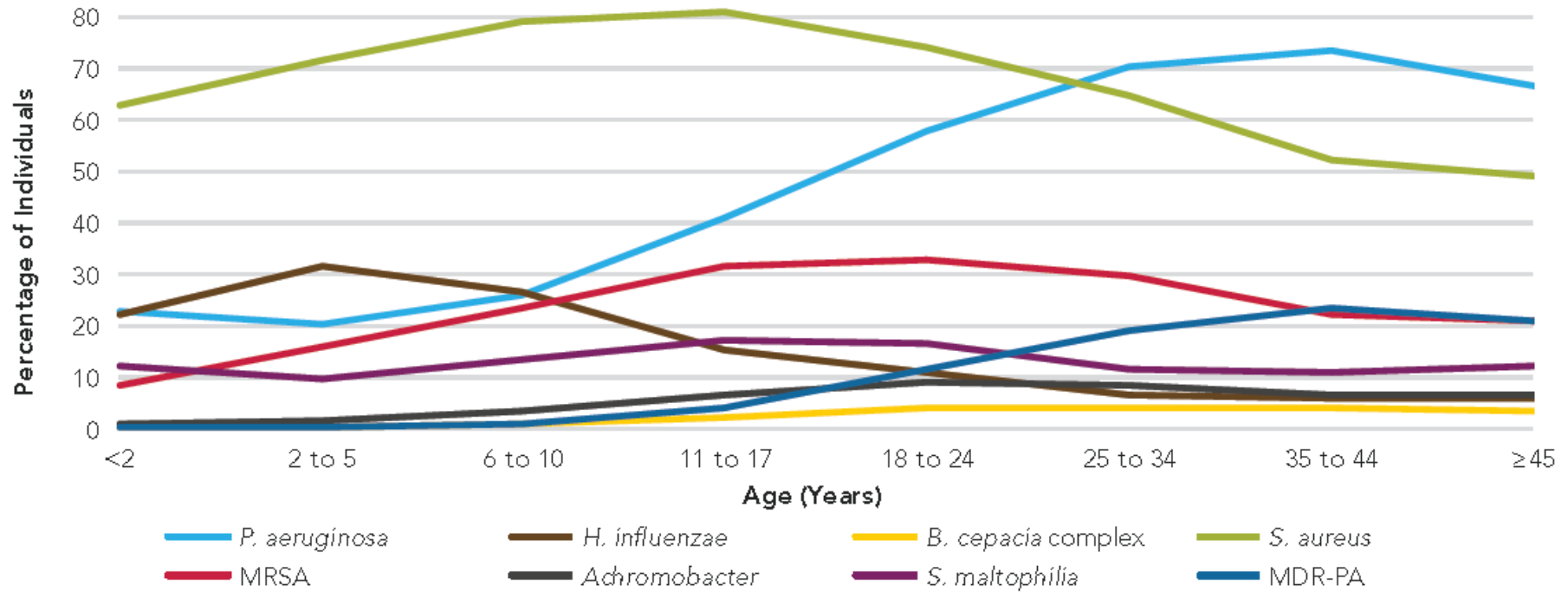
Exacerbation Effects on Microbiome

Intravenous antibiotics for pulmonary exacerbations in people with cystic fibrosis (Review)

Hurley MN, Prayle AP, Flume P

Authors' conclusions

The quality of evidence comparing intravenous antibiotics with placebo is poor. No specific antibiotic combination can be considered to be superior to any other, and neither is there evidence showing that the intravenous route is superior to the inhaled or oral routes. There remains a need to understand host-bacteria interactions and in particular to understand why many people fail to fully respond to treatment.

Susceptibility Testing of *Pseudomonas aeruginosa* Isolates and Clinical Response to Parenteral Antibiotic Administration

Lack of Association in Cystic Fibrosis

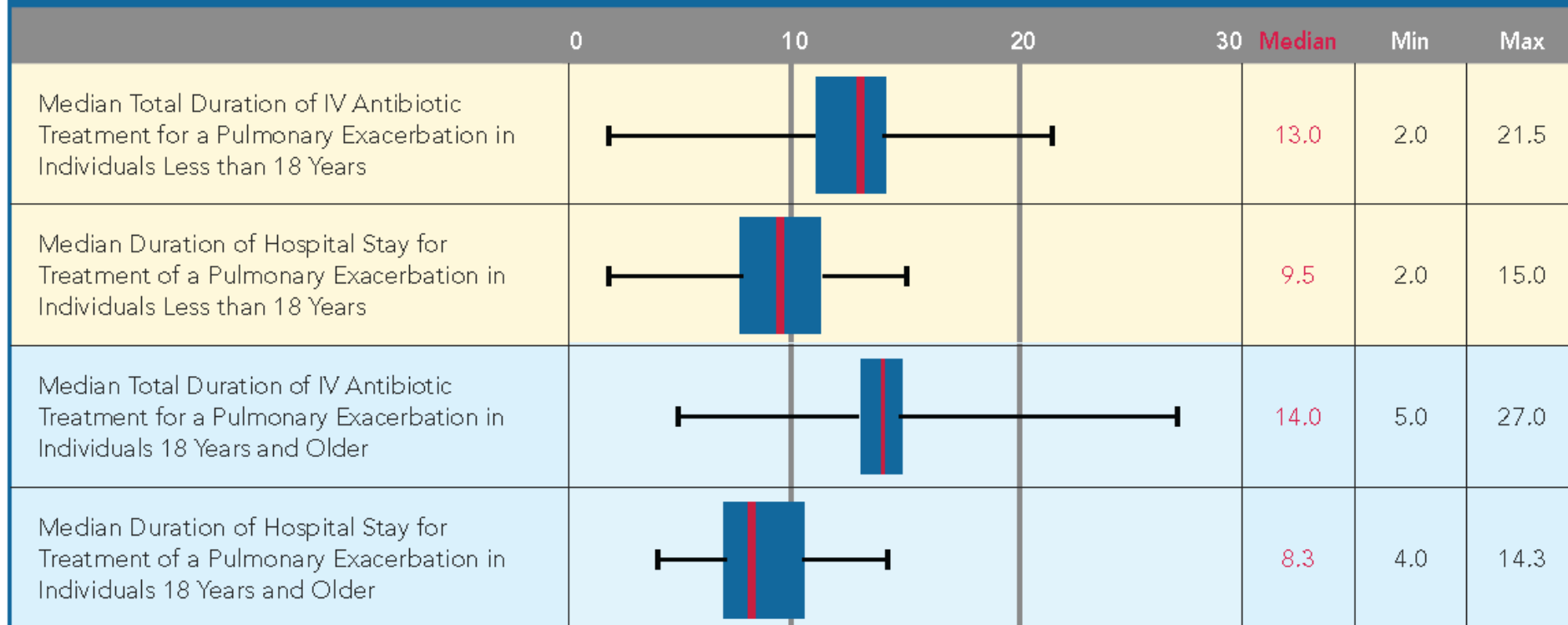Arnold L. Smith, MD; Stanley B. Fiel, MD, FCCP; Nicole Mayer-Hamblett, PhD; Bonnie Ramsey, MD; and Jane L. Burns, MD

Pulmonary function vs. tobramycin or ceftazidime susceptibility

N=77

Smith *et al. Chest* 2003;**123**:1495-1502
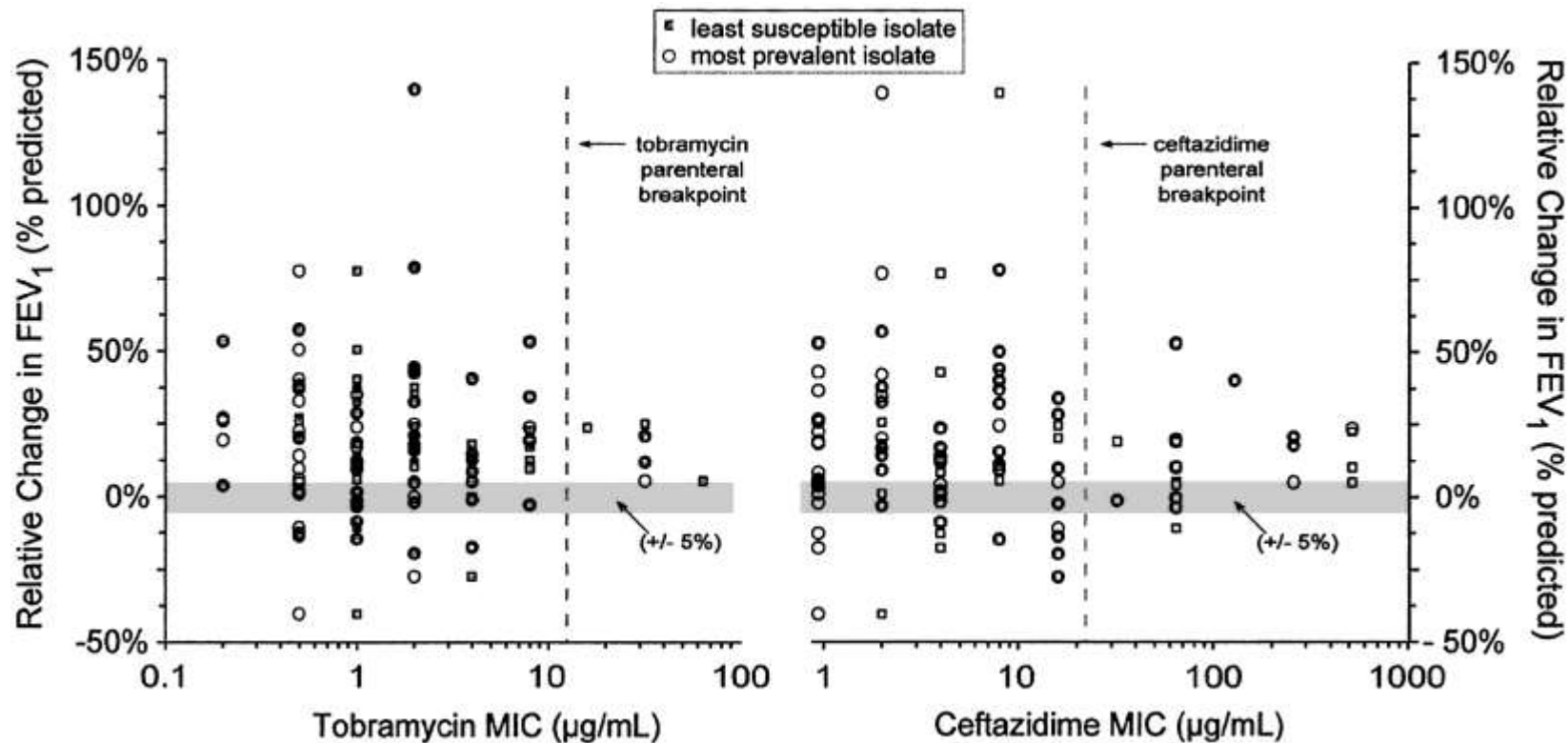
HOW LONG TO TREAT?

Duration of Pulmonary Exacerbation Treatment in Days, by Center

	0	10	20	30	Median	Min	Max
Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals Less than 18 Years					13.0	2.0	21.5
Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals Less than 18 Years					9.5	2.0	15.0
Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals 18 Years and Older					14.0	5.0	27.0
Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals 18 Years and Older					8.3	4.0	14.3

CFF Patient Registry -2015

Duration of intravenous antibiotic therapy in people with cystic fibrosis (Review)

Plummer A, Wildman M, Gleeson T

Data collection and analysis

No eligible trials were identified.

How Long to Treat ?

N=1327

Collaco et al. Am J Respir Crit Care Med. 2010;182(9):1137-43.
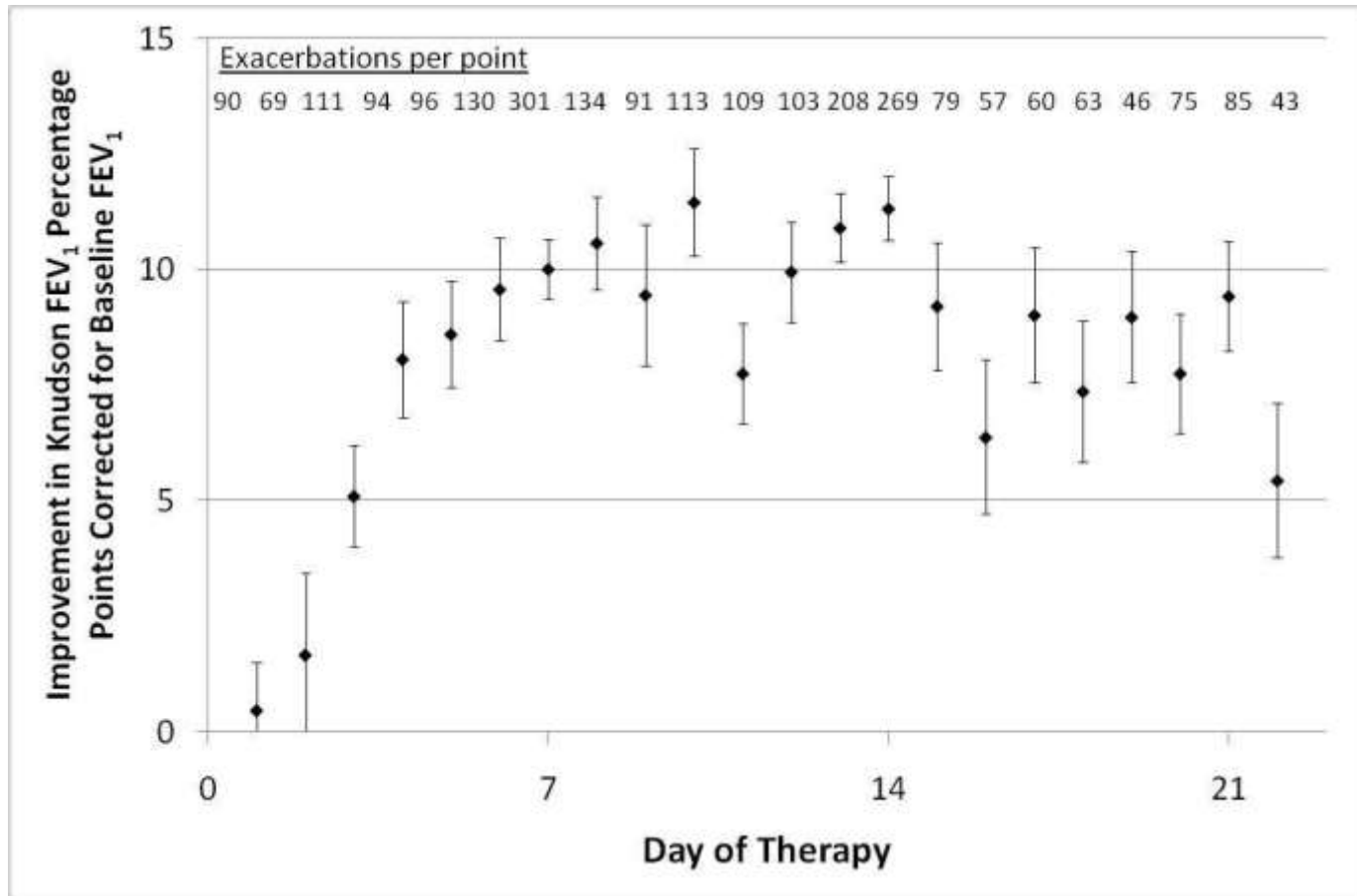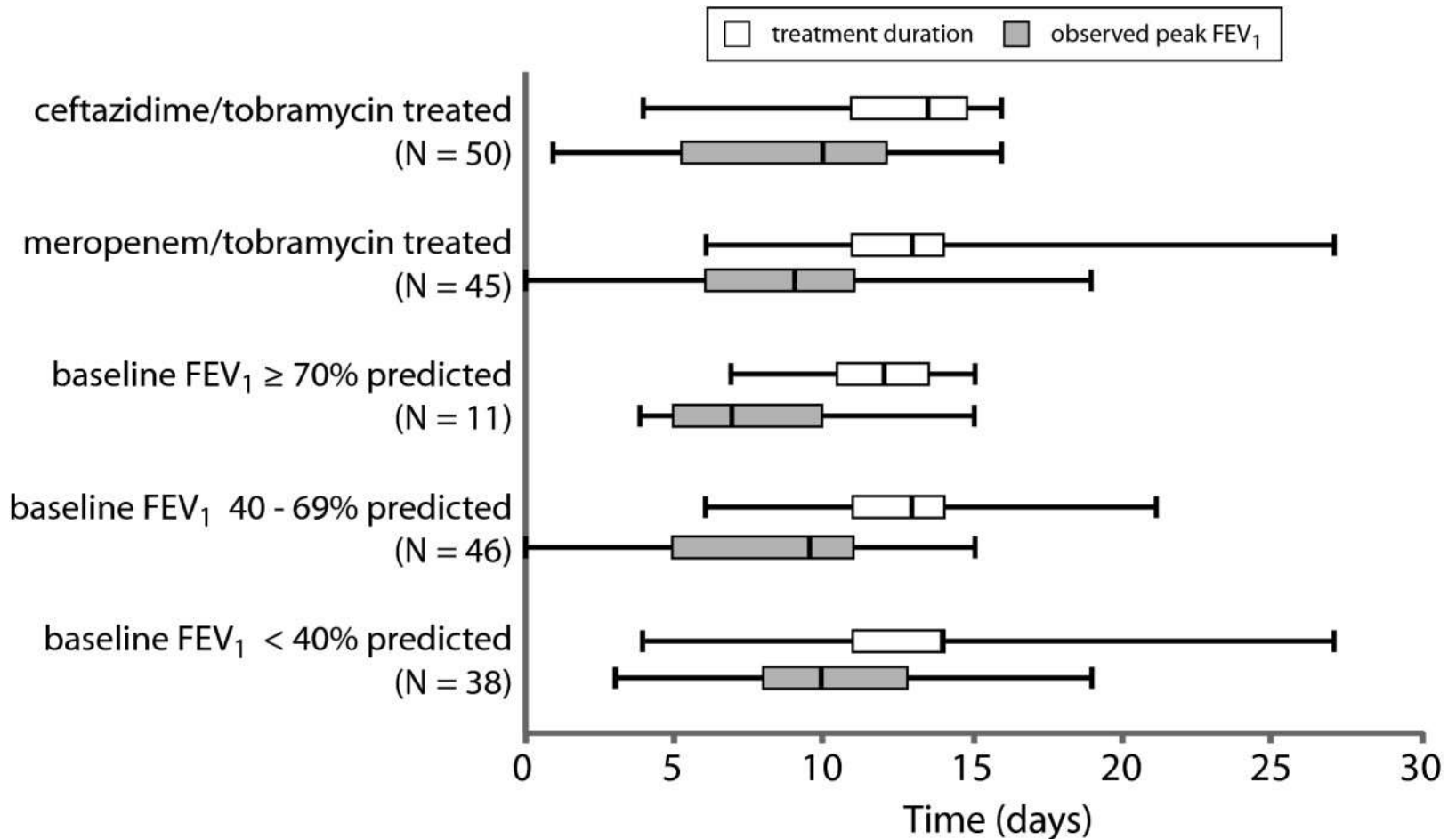
Duration of Therapy

N=1327
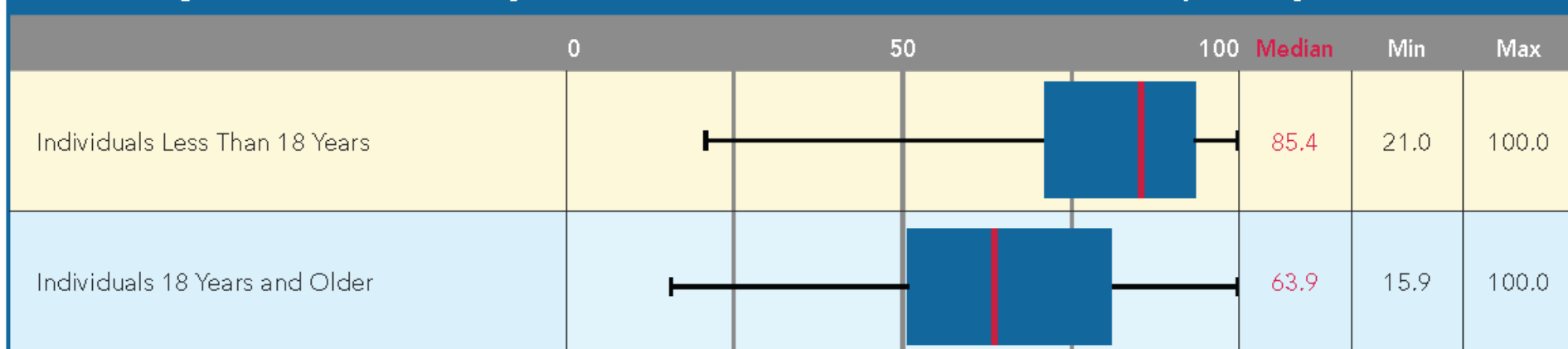
Duration of Therapy

N=95

Site of Treatment

Percentage of Total Pulmonary Exacerbation Treatment Duration in Hospital, by Center

	0	50	100	Median	Min	Max
Individuals Less Than 18 Years				85.4	21.0	100.0
Individuals 18 Years and Older				63.9	15.9	100.0

CFF Patient Registry -2015

Home intravenous antibiotics for cystic fibrosis (Review)

Balaguer A, González de Dios J

THE COCHRANE COLLABORATION®

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Publishers Since 1807

Authors' conclusions

Current evidence is restricted to a single randomized clinical trial.

It suggests that, in the short term, home therapy does not harm individuals, entails fewer investigations, reduces social disruptions and can be cost-effective.

There were both advantages and disadvantages in terms of quality of life.

The decision to attempt home treatment should be based on the individual situation and appropriate local resources.

More research is urgently required.

Cochrane Database of Systematic Reviews

Home versus hospital intravenous antibiotic therapy for cystic fibrosis (Review)

Balaguer A, González de Dios J

Authors' conclusions

Current evidence is restricted to a single randomized clinical trial.

It suggests that, in the short term, home therapy does not harm individuals, entails fewer investigations, reduces social disruptions and can be cost-effective.

There were both advantages and disadvantages in terms of quality of life.

The decision to attempt home treatment should be based on the individual situation and appropriate local resources.

More research is urgently required.

Hospital vs. Home

Hospital

- Guaranteed medication delivery

- More intense airway clearance provided

- Monitoring for occult problems

- Disease education

- Family/life disruption

- Cost

Home

- Less life disruption

- More autonomy

- Compliance is not assured

- Caregiver/patient fatigue

- Minimal monitoring

Pulmonary Perspective

Cystic Fibrosis Pulmonary Guidelines
Treatment of Pulmonary Exacerbations

Patrick A. Flume[1], Peter J. Mogayzel, Jr.[2], Karen A. Robinson[3], Christopher H. Goss[4], Randall L. Rosenblatt[5], Robert J. Kuhn[6], Bruce C. Marshall[7], and the Clinical Practice Guidelines for Pulmonary Therapies Committee*

TABLE 2. EVALUATION OF THE EVIDENCE

Question	Studies	N	Certainty	Magnitude of Benefit	Grade of Recommendation	Recommendation
Site of treatment*	1 RCT(7)	17	Low		I	Insufficient evidence that hospital and home treatment are equivalent

Home intravenous therapy in cystic fibrosis: a prospective randomized trial examining clinical, quality of life and cost aspects

J.M. Wolter, S.D. Bowler, P.J. Nolan, J.G. McCormack

			Hospital	Home	p-value*
FEV1	% pred	Day 0	44 (20)	39 (17)	0.27
		Day 10	50 (21)	45 (22)	
		Day 21	51 (21)	43 (19)	
FVC	% pred	Day 0	58 (17)	56 (19)	0.30
		Day 10	64 (19)	58 (21)	
		Day 21	66 (19)	58 (22)	

N=17

Table 4. – Home *versus* hospital comparison of QOL outcomes

	Hospital	Home	Total	p-value*
Dyspnoea scores	8.2 (5.4)	5.9 (5.5)	7.1 (5.5)	0.25
Fatigue scores	6.8 (4.6)	3.6 (3.4)	5.4 (4.3)	0.04
Emotional scores	8.6 (8.1)	4.4 (5.2)	6.7 (7.2)	0.11
Mastery scores	5.5 (3.8)	2.6 (3.4)	4.2 (3.8)	0.03
Total score	29.5 (16.5)	16.5 (14.8)	23.6 (16.8)	0.03
Family disruption	4.5 (1.3)	6.2 (1.1)	5.3 (1.5)	0.001
Personal disruption	3.8 (1.3)	5.1 (1.0)	4.4 (1.4)	0.004
Sleep disruption	4.4 (1.6)	6.0 (1.3)	5.1 (1.7)	0.005
Eating disruption	5.9 (1.5)	6.6 (0.6)	6.2 (1.2)	0.07
Total disruption	18.3 (3.3)	23.9 (3.3)	20.8 (4.3)	<0.001

Values are presented as mean, and SD in parenthesis. *: p-values compare magnitudes of changes
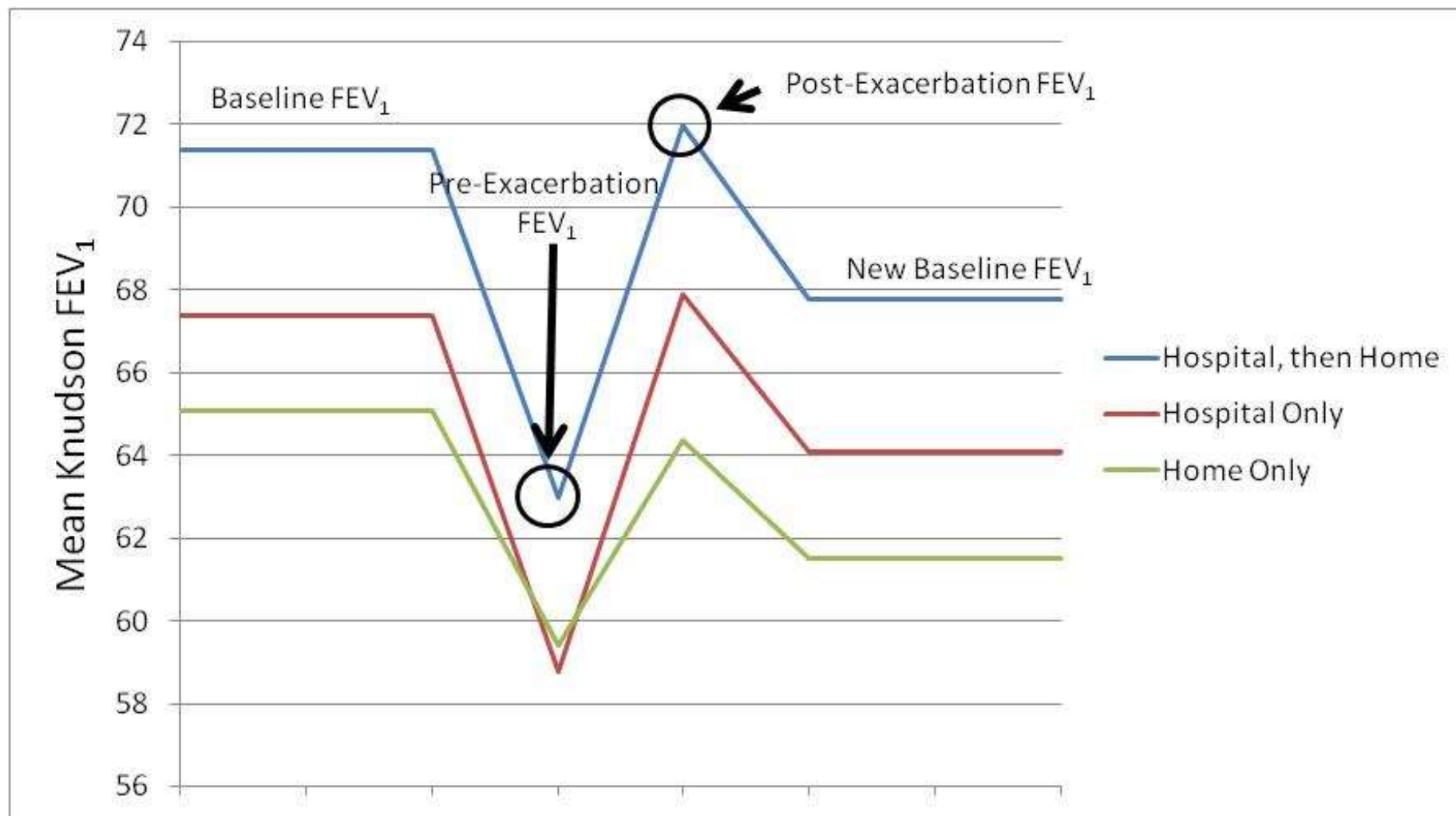
Study	Location	IV Courses (Patients)	FEV$_1$ Outcome
Pond (1994)	UK	51 (25) Paired	Hospital = Home
Bosworth (1997)	USA	32(21) Hospital 27 (19) Home 6(5) Both	Hospital > Home
Riethmueller (2002)	Germany	19(19) Hospital 17 (17) Home	Hospital = Home
Thornton (2004)	UK	241 (51) Hospital 213 (47) Home 18 (18) Both	Hospital > Home
Esmond (2006)	UK	15 (15) Hospital 15 (15) Home	Hospital > Home
Nazer (2006)	USA	64 (27) Hospital 79 (23) Home	Hospital > Home
Termoz (2008)	France	150 (52) Hospital 958 (270) Home 52 (54) Both	Hospital > Home

Home vs. Hospital

		All	Hospital Only	Home Only	Combination: Hospital and Home	P Value (Hospital vs. Home)*
Data by Subject	Number of subjects	479	261	114	248	—
	Mean courses of antibiotics per subject in dataset	2.7 ± 2.4	—	—	—	—
	Age at most recent FEV$_1$ (yr) (mean ± SD)	19.4 ± 8.3	18.2 ± 6.5	22.3 ± 9.4	20.4 ± 9.0	<0.0001
	Sex (% male)	47.4	49	34.2	44	0.01
	CFTR (% F508del homozygotes)	49.2 (n = 478)	51.2 (n = 260)	43	48.6 (n = 247)	0.35
Data by Therapy Course	Number of courses	1,278	602	232	444	—
	Age at start of therapy (yr) (mean ± SD)	17.8 ± 8.0	16.2 ± 6.1	22.0 ± 10.0	17.8 ± 8.2	<0.0001
	P. aeruginosa (% positive)	96.4	95.7	97.8	96.6	0.14
	B. cepacia (% positive)	10.6	11.5	9.9	9.9	0.52
	Days treated in hospital (mean ± SD)	—	12.7 ± 5.3	—	6.0 ± 4.3	—
	Days treated at home (mean ± SD)	—	—	18.9 ± 7.4	12.5 ± 5.7	—
	Total days of treatment (mean ± SD)	15.8 ± 6.7	12.7 ± 5.3	18.9 ± 7.4	18.5 ± 6.0	<0.0001
	Baseline FEV$_1$ (mean ± SD)	68.4 ± 22.0	67.4 ± 22.4	65.1 ± 22.1	71.4 ± 21.2	0.17
	Pretherapy FEV$_1$ (mean ± SD)	60.4 ± 22.0	58.8 ± 22.0	59.5 ± 22.3	63.0 ± 21.5	0.68
	Posttherapy FEV$_1$ (mean ± SD)	68.7 ± 23.4	67.9 ± 23.3	64.4 ± 23.5	72.0 ± 23.0	0.05
	New baseline FEV$_1$ (mean ± SD)	64.9 ± 23.3	64.1 ± 23.1	61.5 ± 23.5	67.8 ± 23.3	0.15

* These P values reflect the difference between the hospital and home categories. P values were determined using Student t and chi-square tests.

Collaco *et al. Am J Respir Crit Care Med.* 2010;182(9):1137-43.

Home vs. Hospital

n=1278

Collaco *et al. Am J Respir Crit Care Med.* 2010;182(9):1137-43.

Home vs. Hospital

Mean ± SD (95% CI)		Hospital Only (n = 602 courses of therapy)	Home Only (n = 232 courses of therapy)	P Value
All courses from Table 1 (n = 602 hospital-only courses and 232 home-only courses)	Sick decline = (pre-FEV$_1$ − baseline FEV$_1$)	−8.6 ± 11.2 (−9.5 to −7.7)	−5.6 ± 7.8 (−6.6 to −4.6)	0.0001
	Immediate recovery = (post-FEV$_1$ − pre-FEV$_1$)	9.2 ± 12.4 (8.2 to 10.2)	5.0 ± 9.3 (3.8 to 6.1)	<0.0001
	Baseline change = (new baseline − baseline)	−3.3 ± 8.4 (−3.9 to −2.6)	−3.5 ± 7.6 (−4.5 to −2.5)	0.69
	Days until next exacerbation: median (interquartile range)	119 (55 to 221) (n = 517)	98 (49 to 204) (n = 198)	0.29

Hospital versus home treatment of respiratory exacerbations in cystic fibrosis

Moran Lavie[ABCDEF]*, **Daphna Vilozni**[BCDE]*, **Gil Sokol**[BD], **Raz Somech**[BD], **Amir Szeinberg**[BD], **Ori Efrati**[ACDEF]

* Moran Lavie and Daphna Vilozni equally contributed to this work

Pediatric Pulmonary Unit and the National Center for Cystic Fibrosis, Edmond and Lily Safra Children Hospital, Sheba Medical Center, Tel Hashomer, Israel

Table 2. Mean percent change in spirometry indices in each of the treatment setting. There was no statistical difference between the groups.

% change ±SD	Home treatments n=55	Hospital treatments N=84	P value
FVC	12.2±17.5	8.8±16.9	0.2574
FEV1	14.3±34.4	14.26±20.2	0.9989
PEF	14.1±27.5	9.0±19.3	0.2010
FEF25–75	8.1±22.6	16.0±25.2	0.0620

- Mean duration of treatment was 9.7±6.7 days for the hospital site and 16.3±9.1 days for the home site (P<0.02).
- Dramatic differences in patients with CFRD

Lavie *et al. Med Sci Monit,* 2011; 17(12): CR698-703

N=54

The CF Foundation recommends against delivery of intravenous antibiotics in a nonhospital setting unless resources and support equivalent to the hospital setting can be assured for the treatment of an acute exacerbation of pulmonary disease.

- Grade I recommendation

Factors to Consider for Home Therapy

- Ability to perform infusions and airway clearance
- Availability of caregiver support
- Social issues
  - Impact of family members
  - School/work absence
- Financial issues
  - Loss of wages
  - Cost

Ivacaftor – STRIVE Study
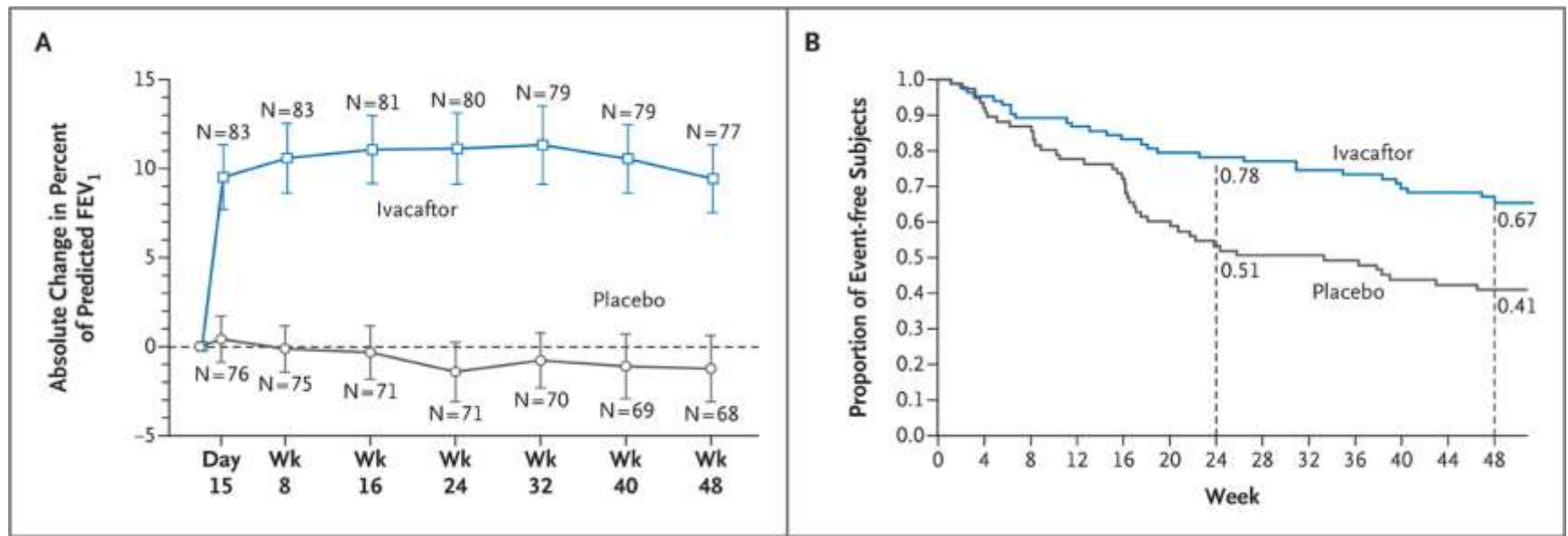
Lumacaftor & Ivacaftor

Lumacaftor & Ivacaftor

Note: Pooled analysis of TRAFFIC and TRANSPORT

©2014 Vertex Pharmaceuticals In

Wainwright *et al. NEJM*. 2015, **373**(3):220-231
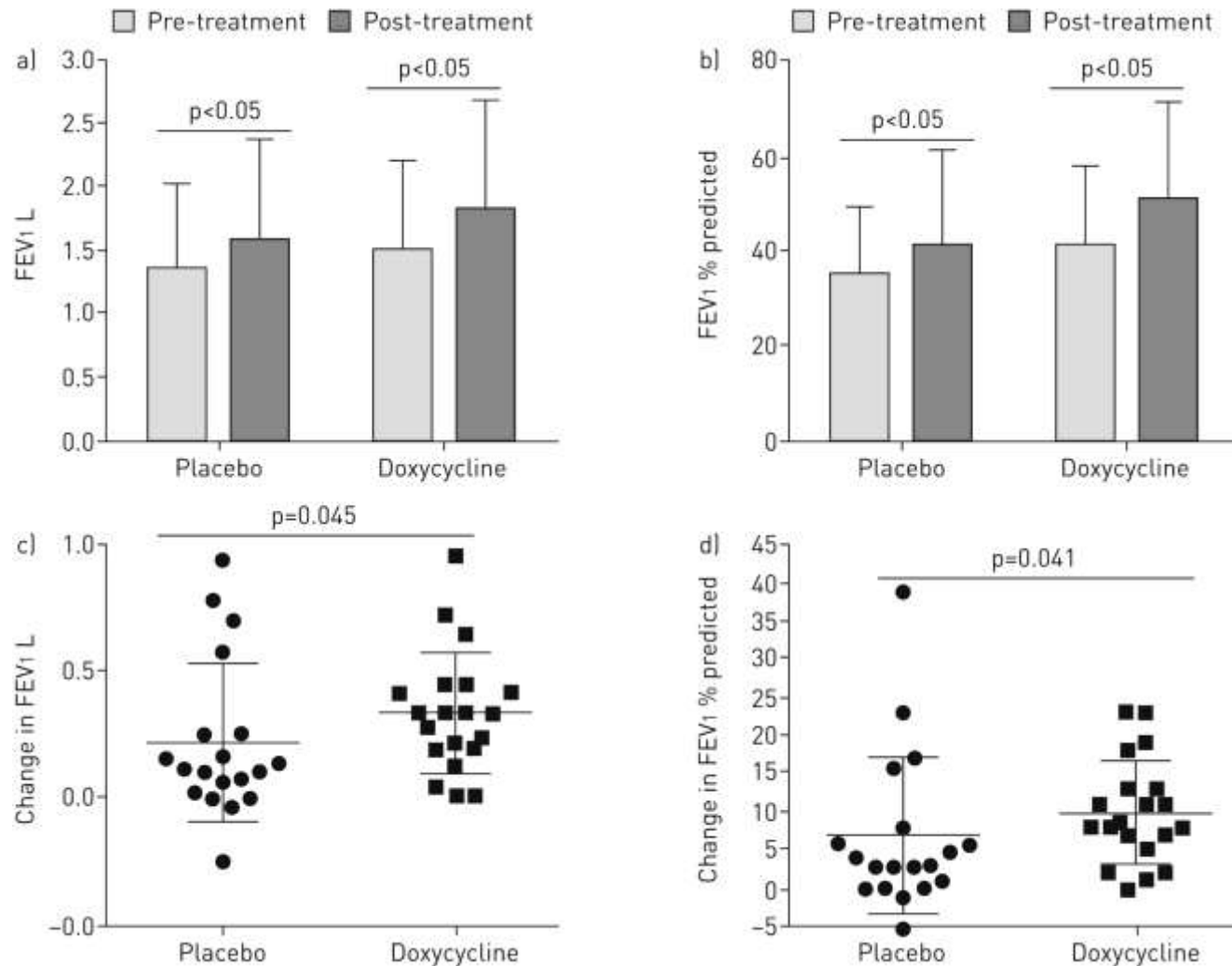
Ivacaftor Does Not Improve Recovery
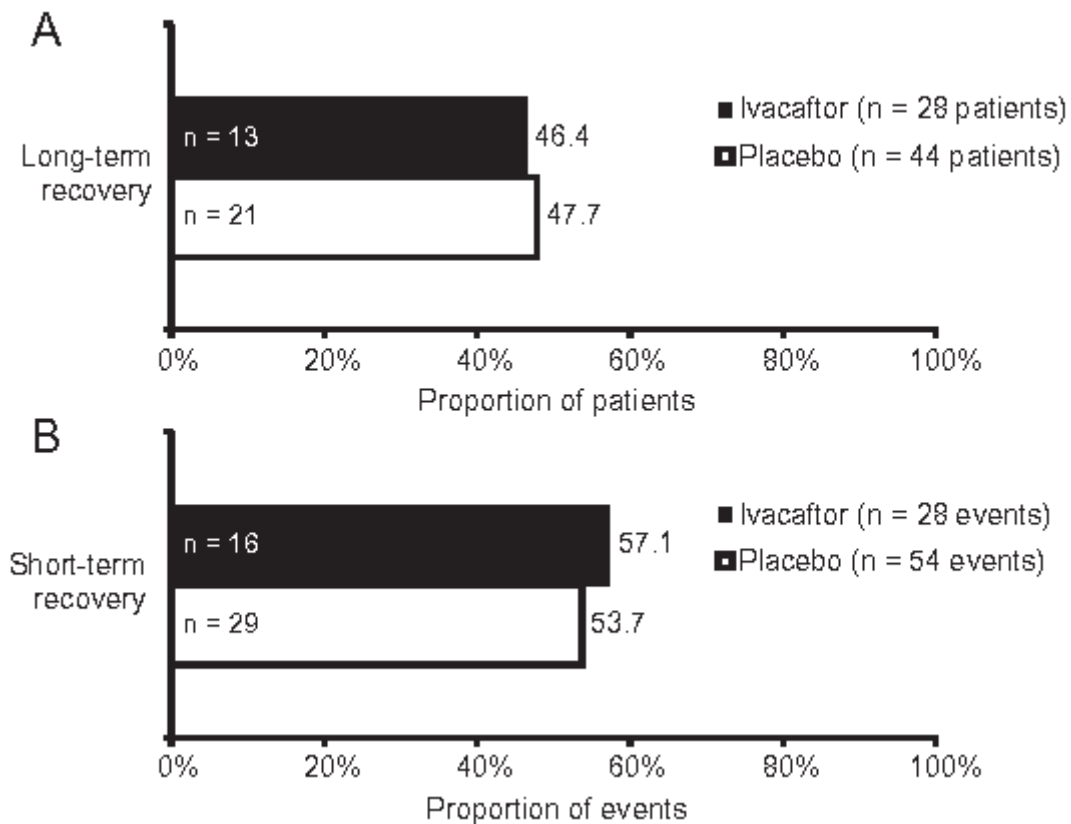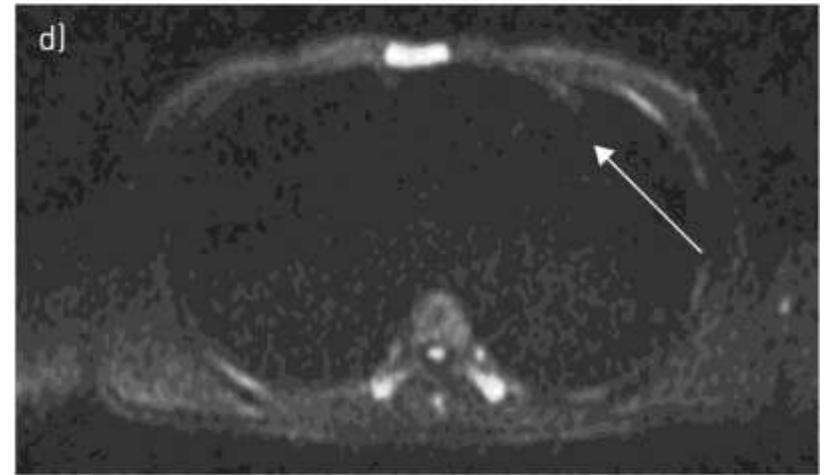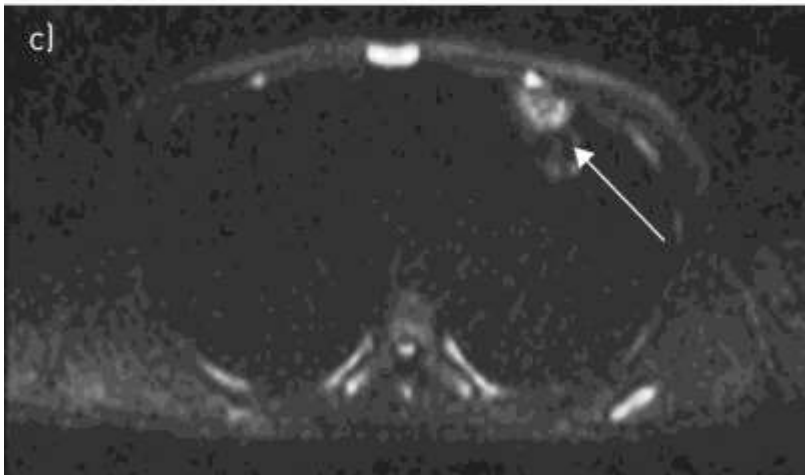

N=161
≥12 years

Doxycycline as Adjunctive Treatment
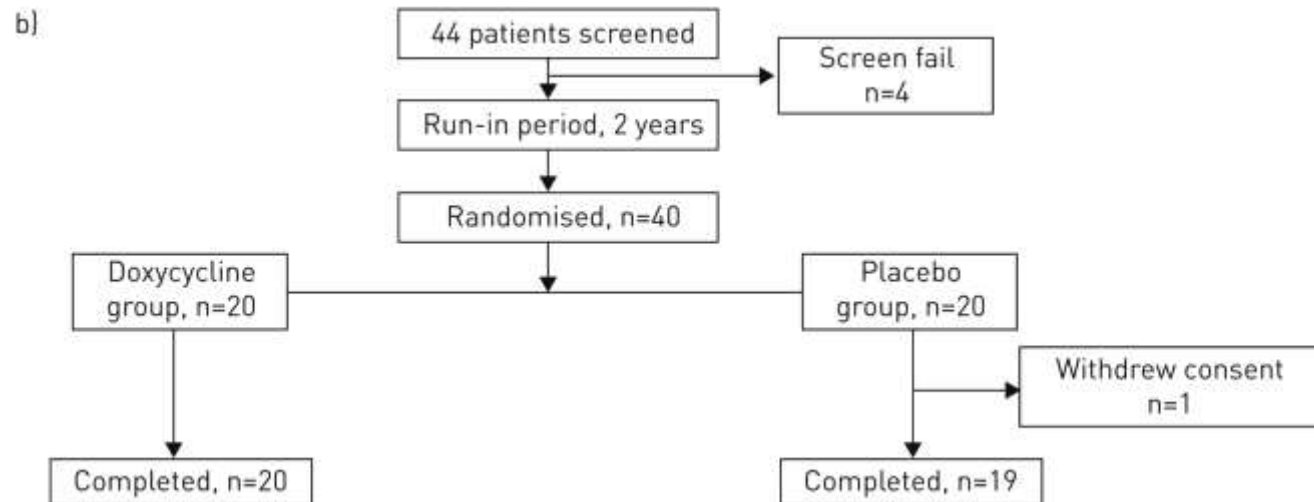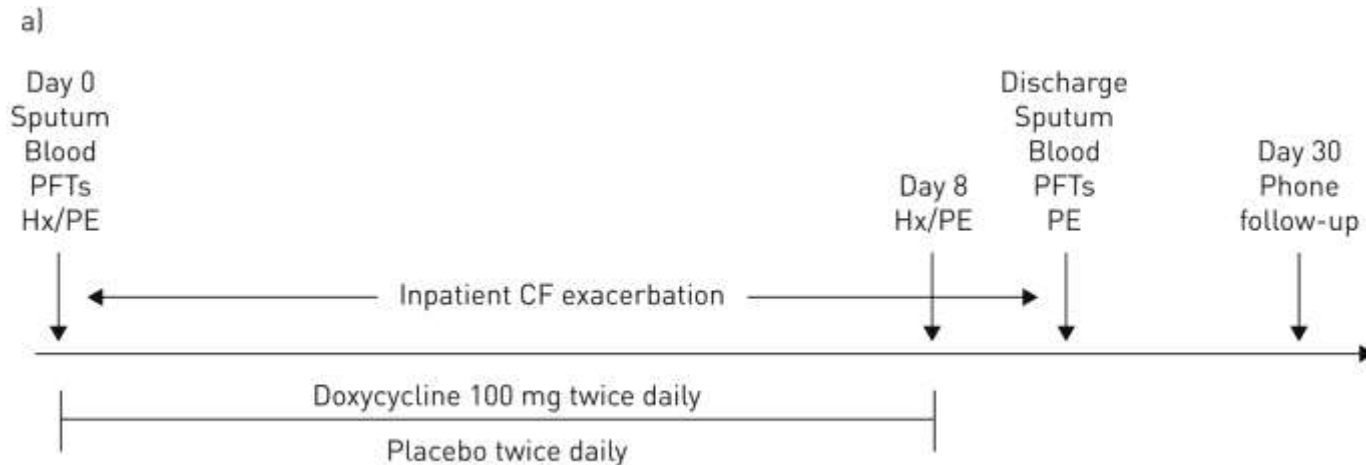
Xin Xu et al. Eur Respir J 2017;49:1601102

Doxycycline as Adjunctive Treatment

Xin Xu et al. Eur Respir J 2017;49:1601102

Doxycycline as Adjunctive Treatment

Xin Xu et al. Eur Respir J 2017;49:1601102
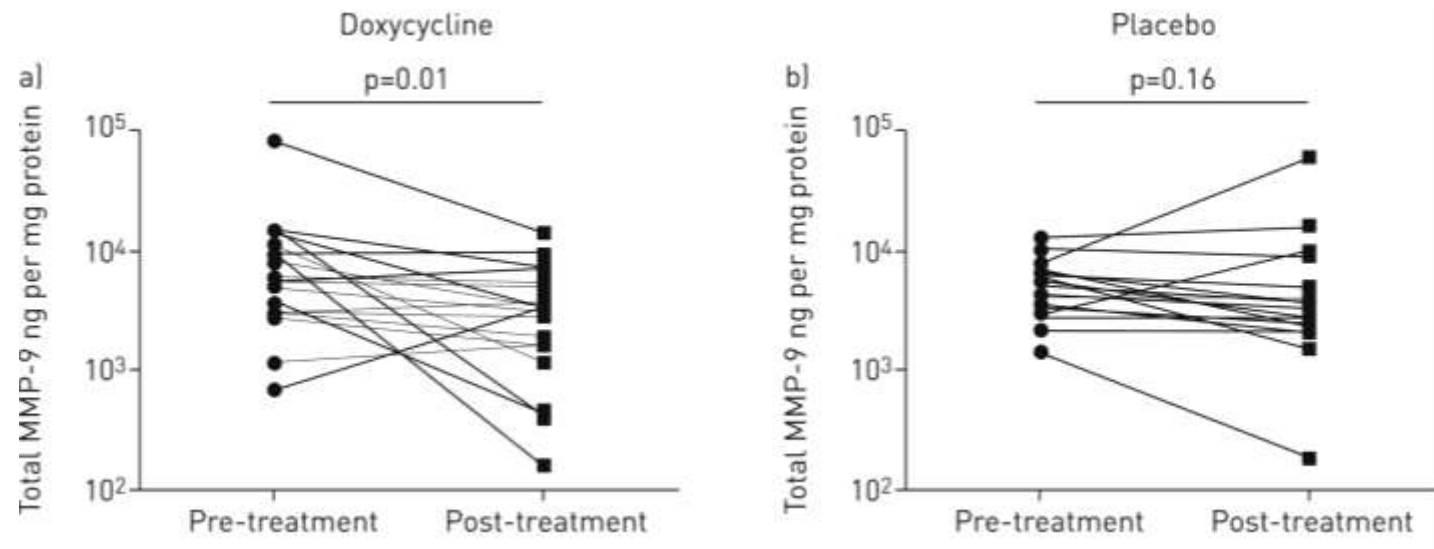
Relation between morphological changes and Inflammation Using Diffusion-Weighted MRI
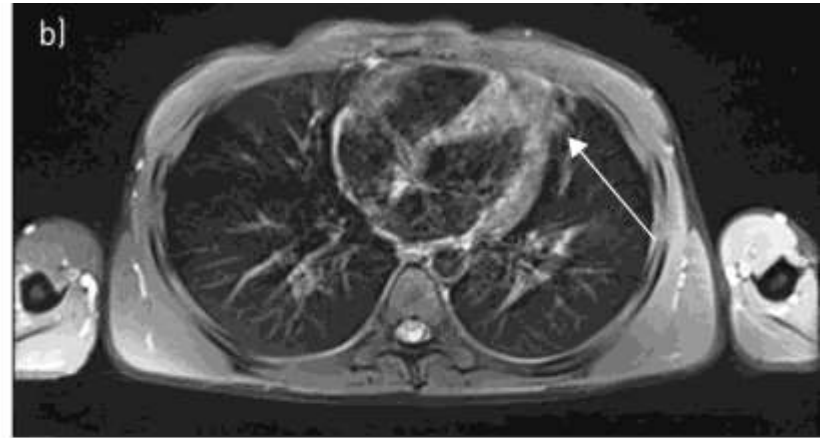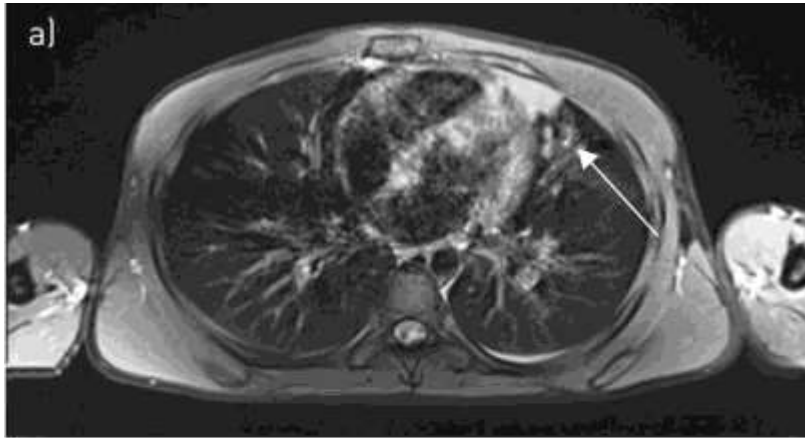
Pre-treatment

Post-treatment

Home Spirometery

	Spirometry	Usual Care	p
Acute Visits meeting protocol defined PE, n (%)	108 (71%)	44 (69%)	0.871
Requiring Oral Antibiotics	72 (67%)	19 (43%)	0.010
Requiring IV Antibiotics	35 (32%)	23 (52%)	0.027
Requiring Inhaled Antibiotics	16 (15%)	10 (23%)	0.244
Requiring Any Antibiotics	91 (84%)	39 (89%)	0.615
Requiring Hospitalization	31 (29%)	22 (50%)	0.015

Lechtzin *et al. Am J Respir Crit Care Med.* 2017 Jun 13.

Home Spirometery

Lechtzin *et al. Am J Respir Crit Care Med.* 2017 Jun 13.
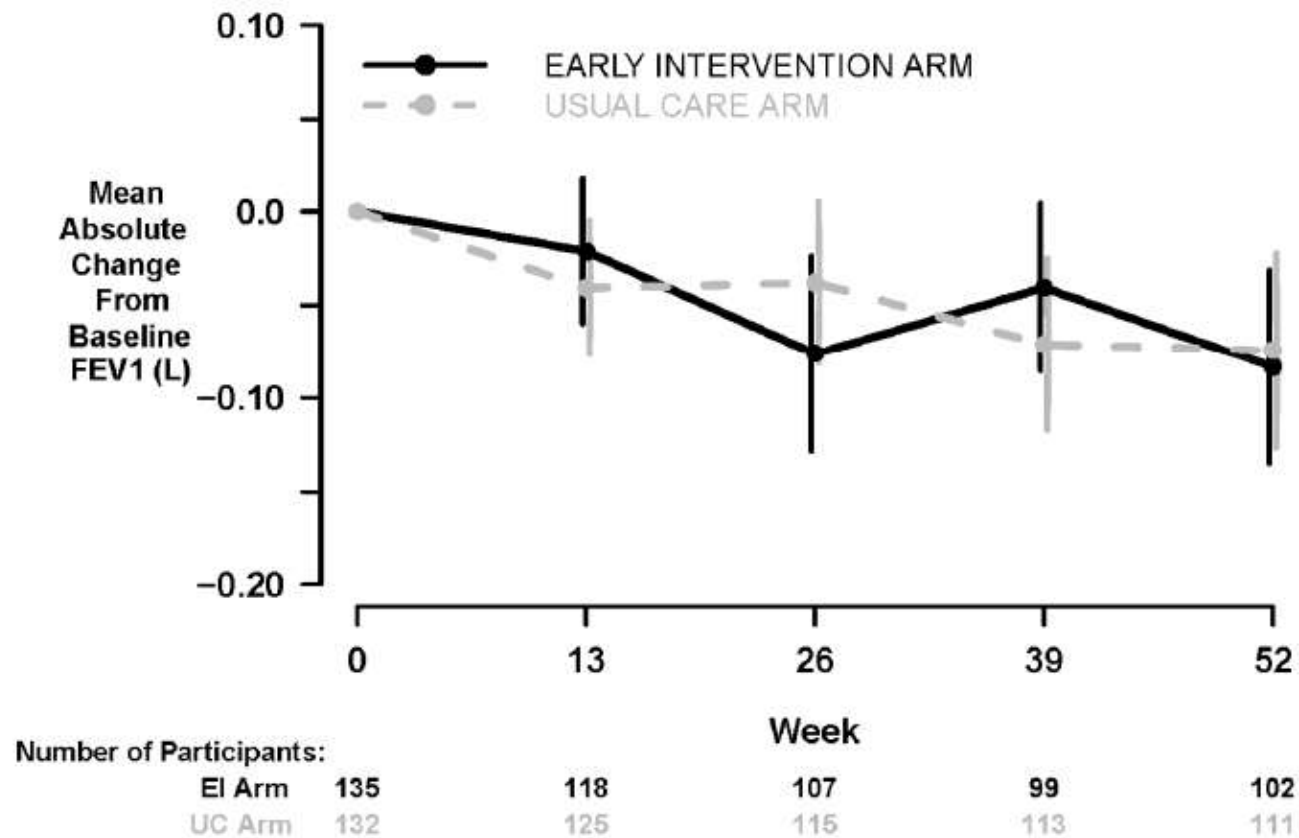
Final Thoughts

- Exacerbations are a significant source of morbidity for patients with CF

- Determining optimal approaches to exacerbation therapy is a vitally important but poorly studied

- Optimal choice and length of therapy is unknown and, therefore, decisions should be made on an individual basis

- Home exacerbation therapy can be successful in properly selected cases

eCysticFibrosisReview.org

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MEDICINE

eLITERATURE REVIEW

eCysticFibrosis Review

Presented by
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