Inhaled Antibiotics in Cystic Fibrosis

-current state and future considerations

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Disclosures

Active independent research funding

NIH (NHLBI, NIDDK), CF Foundation, Gilead Sciences, Grifols

Consultation

Wide variety of Industry sponsors engaged in CF research, some of whom are developing or have developed inhaled antimicrobial drugs.

Outline: 3 Key Topics

1. What's happening now?

   -current state of CF care and inhaled antibiotic use

2. What's needed most?

   -focus of unmet need in inhaled antimicrobials

3. What's feasible and informative to the CF community?

   -key issues in study design

Inhaled Antibiotics in CF

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Inhaled tobramycin and inhaled aztreonam are the only two inhaled antibiotics with FDA approval.

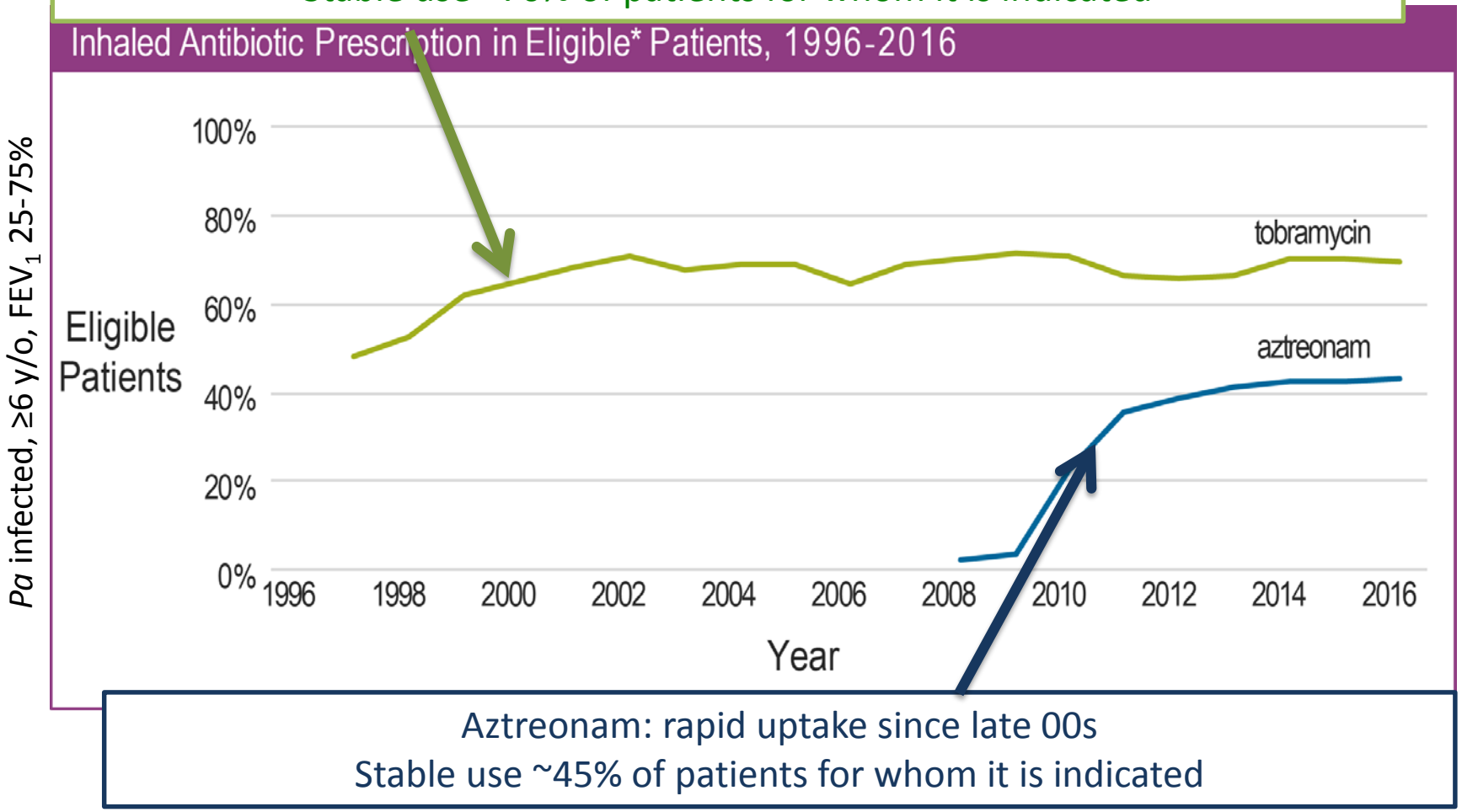
Developed nearly 20 and 10 years ago, respectively

Target the same pathogen (*P. aeruginosa*)

Consensus opinion of ongoing clinical benefits and high prescription rates for both drugs

Inhaled tobramycin and aztreonam

Tobramycin: rapid uptake since late 90s
Stable use ~70% of patients for whom it is indicated

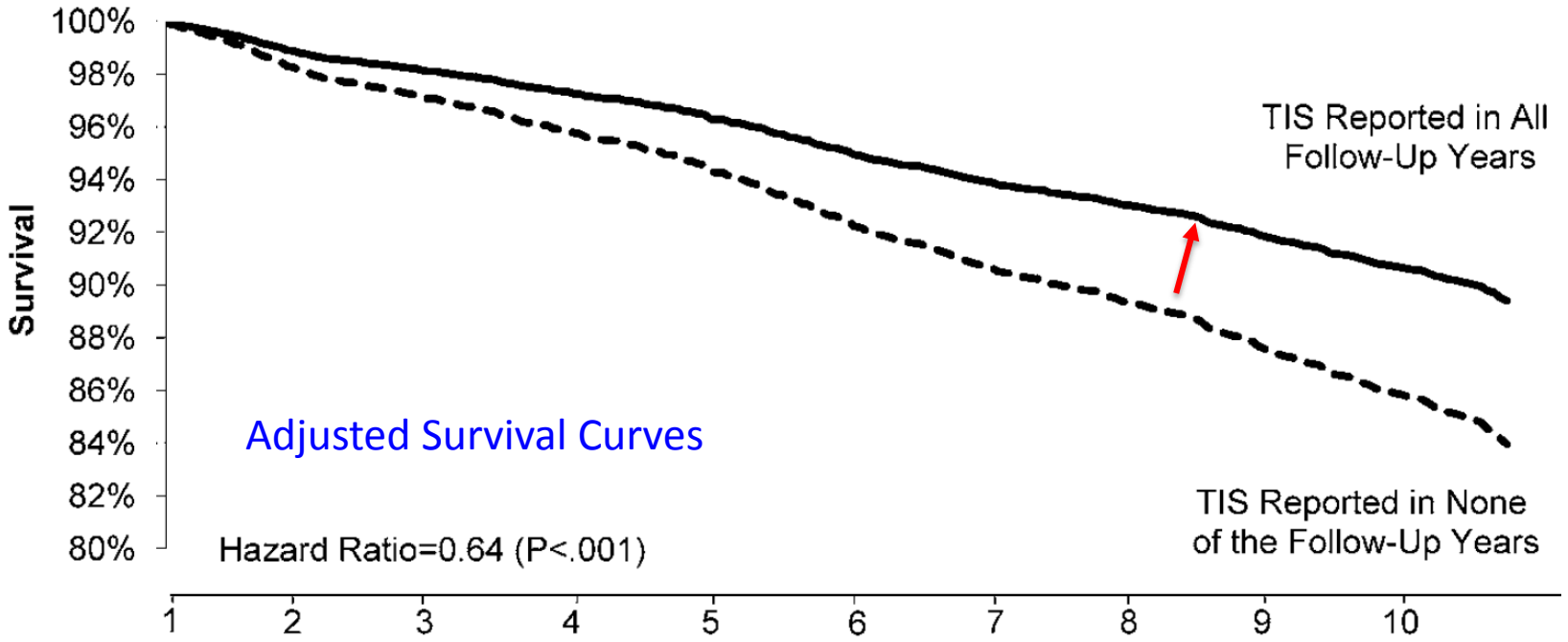


Aztreonam: rapid uptake since late 00s
Stable use ~45% of patients for whom it is indicated

US CF National Patient Registry Report 2016

Long-term clinical use (TOB) associates with improved survival

(US CF Patient Registry 1996-2008)

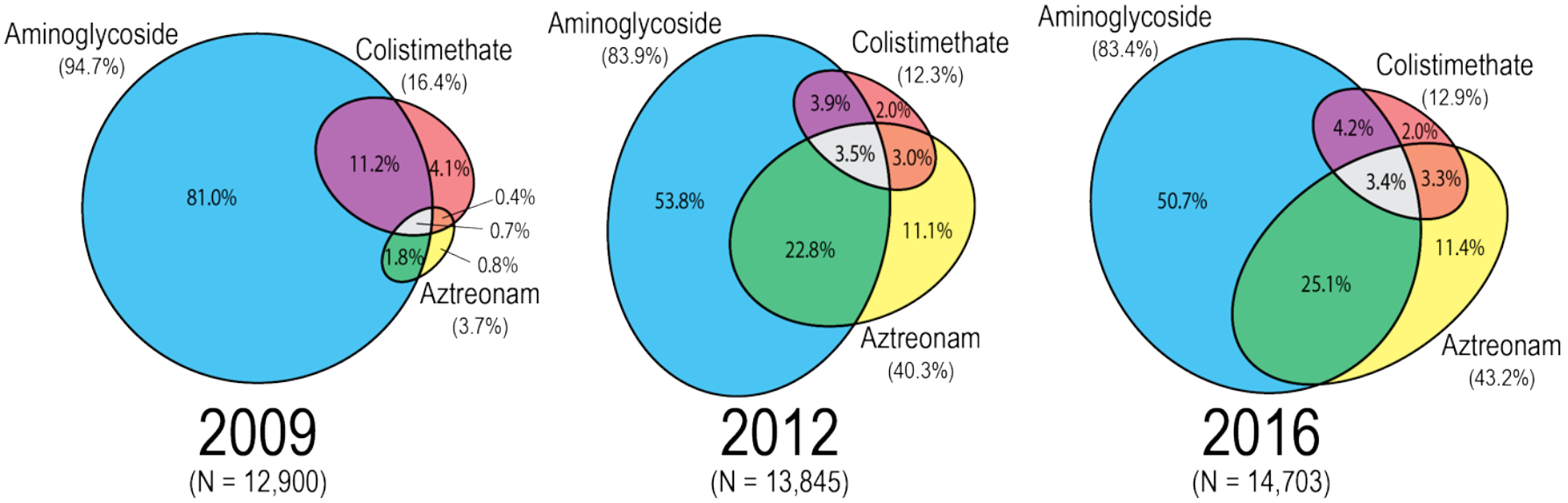


	2-year mortality	5-year mortality	10-year mortality
TIS user	1.3%	5.2%	9.9%
TIS non-user	2.1%	8.0%	15.0%

Pediatr Pulmonol 2012; 47:44-52

Inhaled Antibiotics in CF

– Use patterns (in US)



J Cyst Fibros 2015 May;14(3):370-5.
2016 US CF National Patient Registry Data

Inhaled Antibiotics in CF

Inhaled antibiotics used for two main purposes:

A. eradicating early *P. aeruginosa* (1 drug for 1 or 2 cycles)

B. chronic suppressive therapy (1+ drugs cycled on/off)

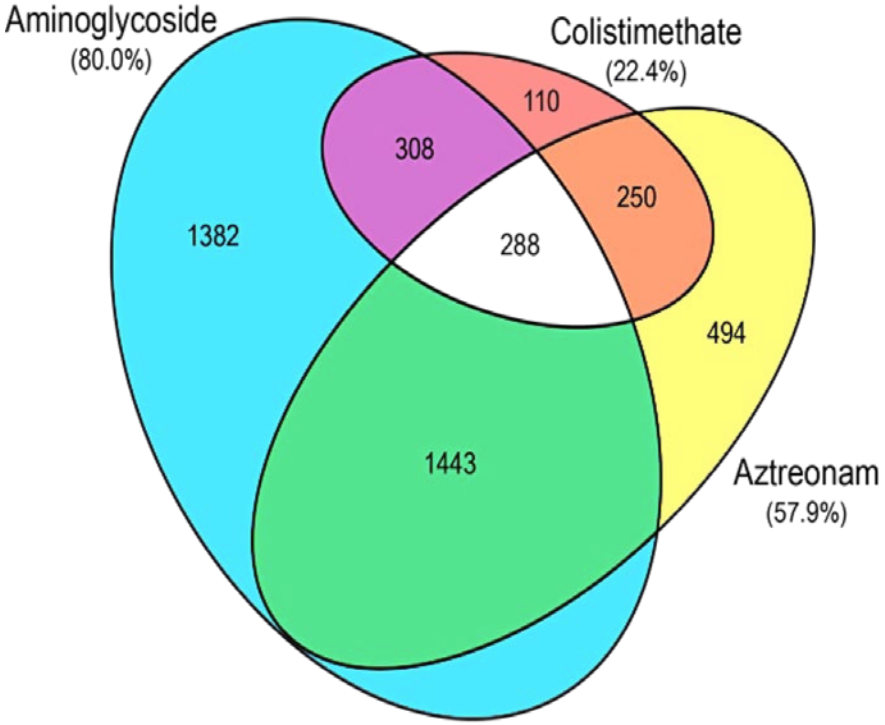
Users of >1 class of inhaled antibiotic (cycled on/on):

- Older age (adolescent and adult ages)
- Lower lung function (FEV_1% ≤70% predicted)
- Multiple *P.a.+* cultures (chronic infection)
- experiencing pulmonary exacerbations

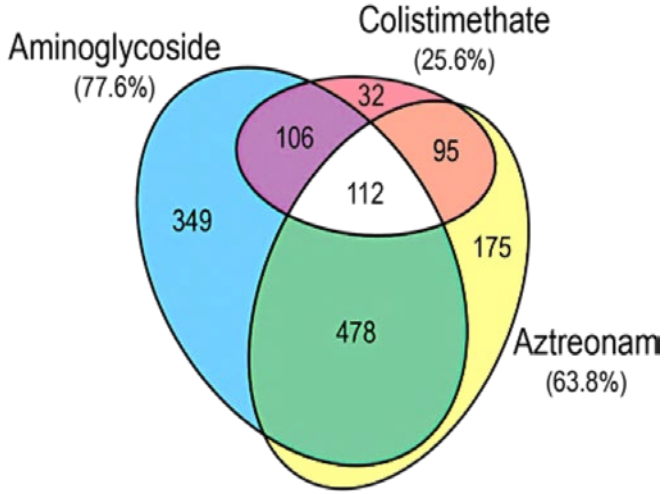
this describes a typical/desirable study population for inhaled antibiotics

2016 CFNPR Data Limited to:

- Age ≥ 12 y/o
- FEV_1% 25-75%
- ≥ 1 acute pulmonary exacerbation



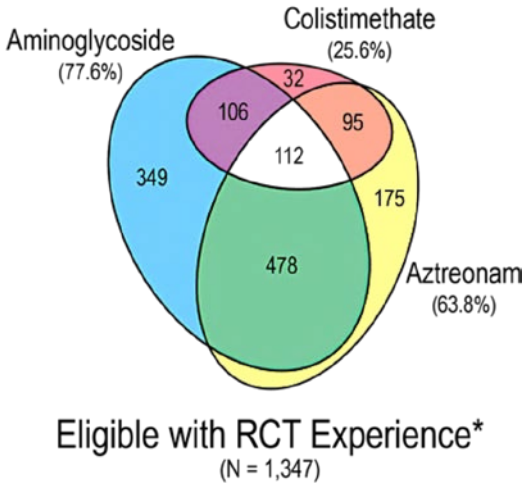
All Eligible
(N = 4,275)



Participated in RCT since 2010

Inhaled Antibiotics in CF

Hypothetical New Drug Study using historical key eligibility criteria:



80% using TOB
60% using AZLI

Majority are cycling multiple drugs to avoid the “off” period

If restrict to RCT participation (i.e. interest & ability):
~800 on continuous alternating therapy (CAT)
~500 cycling on/off TOB or AZLI

Inhaled Antibiotics in CF

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Focus of Unmet Need in CF

Eradication?

Focus of Unmet Need in CF

Eradication? No

-care guidelines and two effective treatment options

-data suggest systemic antibiotics useful for failure to eradicate

Focus of Unmet Need in CF

Eradication? No

Early persistent *P. aeruginosa*?

Focus of Unmet Need in CF

Eradication? No

Early persistent *P. aeruginosa*? No

-two safe, effective antibiotic options for cycled Rx

-multiple drug delivery options

(additional agents would be valued but are not the greatest priority)

Focus of Unmet Need in CF

Eradication? No

Early persistent *P. aeruginosa*? No

Chronic *P.a.* and clinical decline?

Focus of Unmet Need in CF

Eradication? No

Early persistent *P. aeruginosa*? No

Chronic *P.a.* and clinical decline? Yes

-long-term exposure to approved agents

-clinical decline despite common use of (CAT) with both FDA-approved drugs

Focus of Unmet Need in CF

Eradication? No

Early persistent *P. aeruginosa*? No

Chronic *P.a.* and clinical decline? Yes

Other CF pathogens and clinical decline?

Focus of Unmet Need in CF

Eradication? No

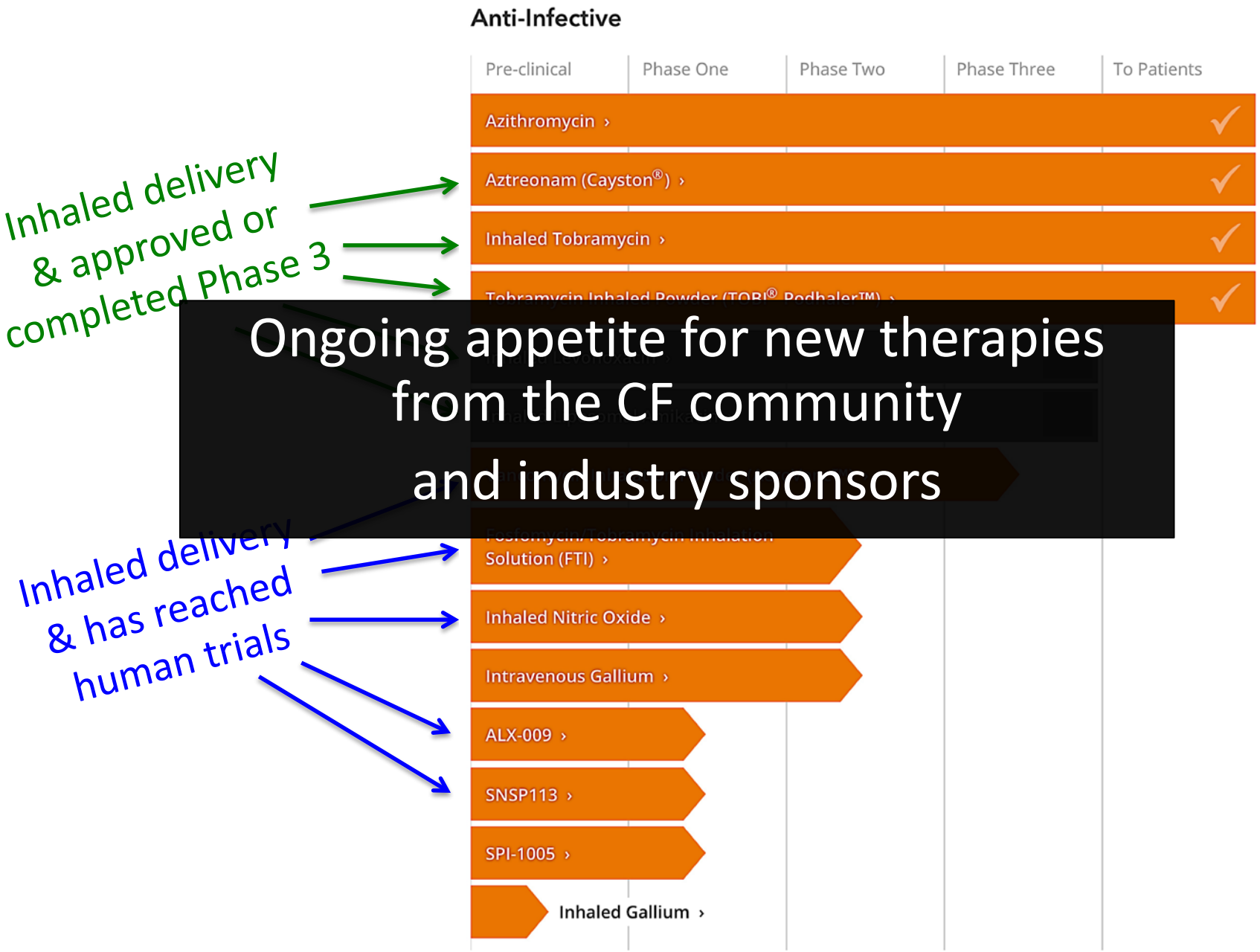
Early persistent *P. aeruginosa*? No

Chronic *P.a.* and clinical decline? Yes

Other CF pathogens and clinical decline? Yes

-but more complicated w/ less certainty about pathogenicity and effect of Rx

-often co-infected with *P.a.*



CFF.org Drug Development Pipeline. Accessed May 2018

Few Points Regarding Special Pathogens

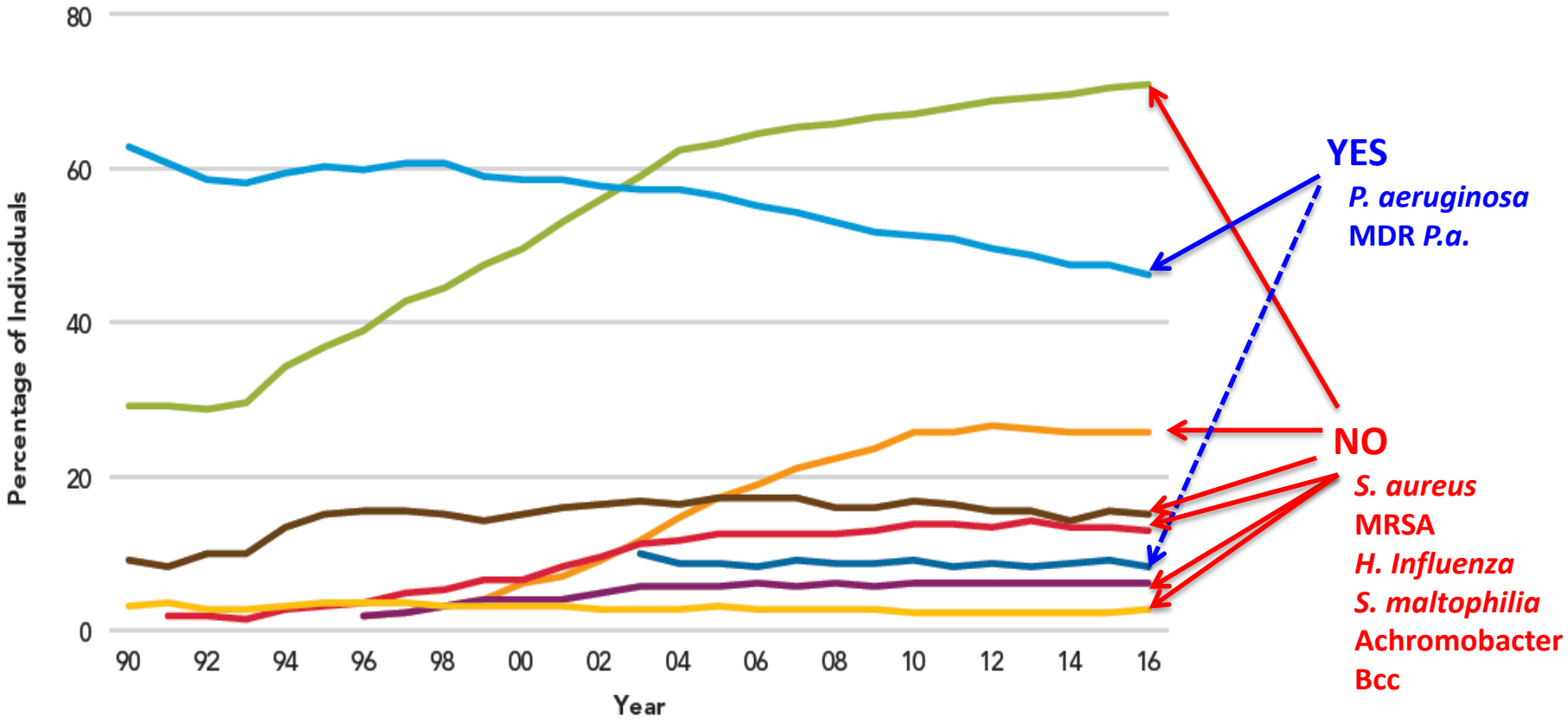
increasing prevalence and no approved drugs

Pathogen	2001	2011	2016
Methicillin resistant *S. aureus* (MRSA)	7.3%	26%	26%
Nontuberculous mycobacteria (NTM)	unknown	10.8%	12.7%
S. maltophilia	8.8%	14%	13.1%
several other rare pathogens or those of more variable clinical impact but often targeted with antibiotics (Achromobacter, Burkholderia, fungi, etc.)			

2016 CFNPR Data. Actual prevalence likely underestimated

Inhaled Antibiotics in CF

FDA approved inhaled antibiotic for Key CF Respiratory Pathogens



CFNPR 2016

Inhaled Antibiotics in CF

Limited FDA-approved options plus perceived clinical need has been accompanied by

inconsistent and unproven off-label drug use for common and less-common pathogen.

Off-label Compounding for Inhalation

Secure | https://www.foundcare.com/fc-patients/compounding-customized-unit-dose-medications/?hilite=%27inhaled%27%2C%27ant...

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CF and **Inhaled** Medications

Foundation Care pharmacists have over 35 years of combined experience in compounding medications for respiratory use. They will work with your physician to find a solution that best suits your needs and lifestyle.

Our compounded medications are placed in ready to use, unit dose neb vials. This provides a quality, sterile compounded product that is both easy and safe for patients to use.

*Many nebulized medications used to treat infections are not available commercially.

Commonly compounded respiratory products include:

- Amikacin
- Gentamicin
- Amphotericin B
- Levofloxacin
- Ceftazidime
- Pentamidine
- Ciprofloxacin
- Tobramycin
- Clindamycin
- Vancomycin
- Colistimethate

The Unmet Need (summary)

1. Limited approved options
   -nothing developed/approved for nearly 10 years
   -largely meeting needs for eradication and early *P.a.*

2. Real focus of need is chronic *P.a.* with clinical decline
   -majority already cycling the 2 FDA-approved drugs

3. Off-label use and full drug development pipeline underscore desire for more safe/effective options

4. Non-*P.a.* pathogens deserve attention and have some unique challenges or uncertainties

Inhaled Antibiotics in CF

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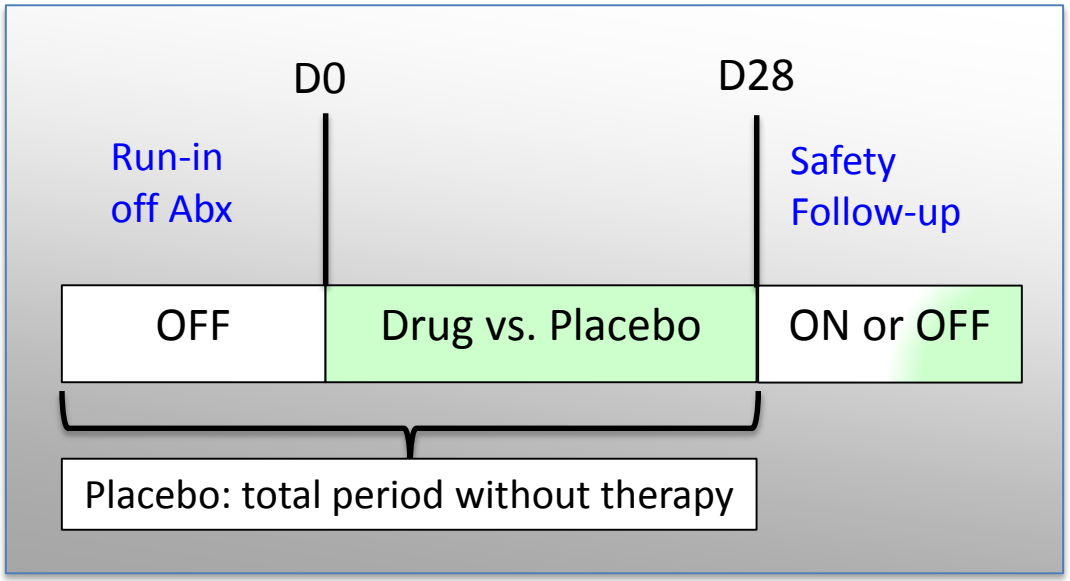
Placebo-controlled trial testing 28 days with new drug:

Length of run-in period:

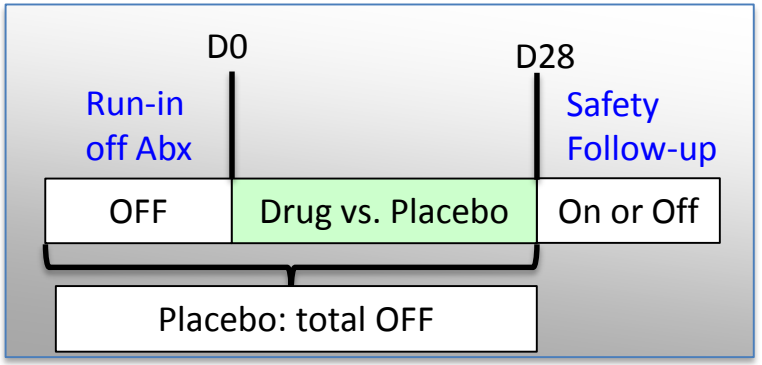
2 weeks = at least 42d without active drug

4 weeks = at least 56d without active drug



Inhaled Antibiotics in CF

Placebo-controlled Trials



-Most eligible patients using CAT

-large studies will be challenging unless CAT users can be recruited

-Small population cycling 1 product go 28d without inhaled Abx

-consider length of run-in period and allowing active drug during follow-up

-stretching designs to 2 or 3 ON/OFF placebo-controlled cycles appears unfeasible

Despite the challenges, shorter placebo-controlled trials of efficacy are possible in the US

Considerations in Study Design

1. Shorter placebo-controlled trials are feasible

2. Blinding is problematic for active comparator trials

Blinded ACT: double dummy, current vs. new drug

1. Recruit population on unified drug and dosing regimen

2. Blinding may fail in group familiar with inhaled products
   - Taste, smell, appearance when nebulized

3. High complexity/burden for both sponsors and participants

Ultimately, not viewed as viable/feasible design

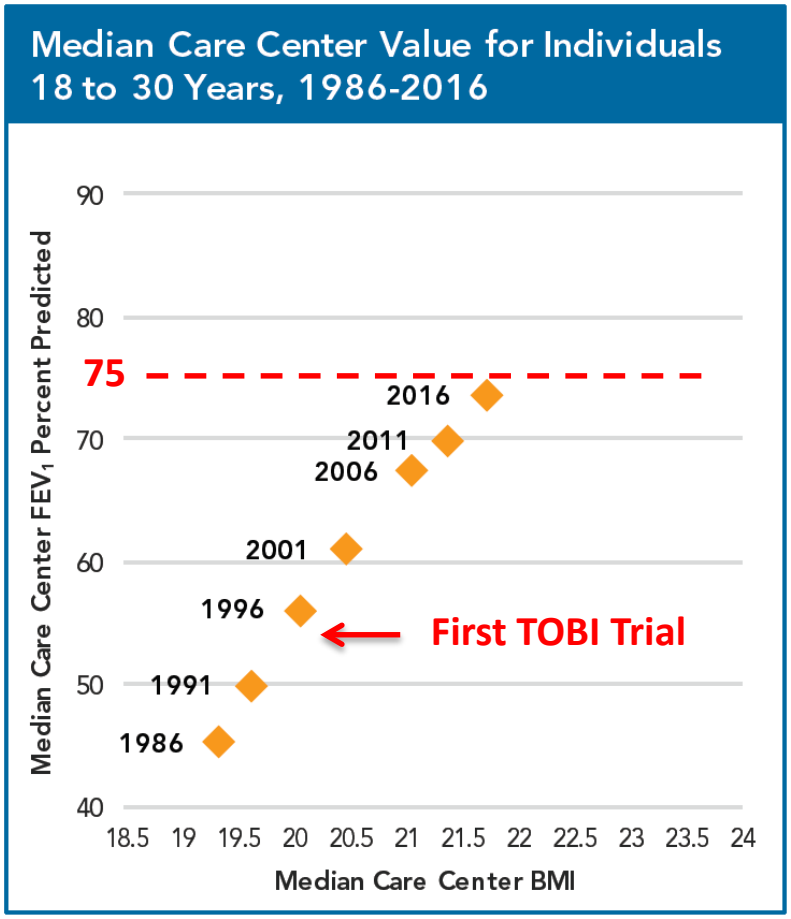
Considerations in Study Design

1. Placebo controlled = short, difficult study

2. Blinding is problematic for active comparator trials

3. Effect sizes in key outcome measures may diminish even for similarly potent antimicrobial drugs

Lung Function (FEV_1pp)



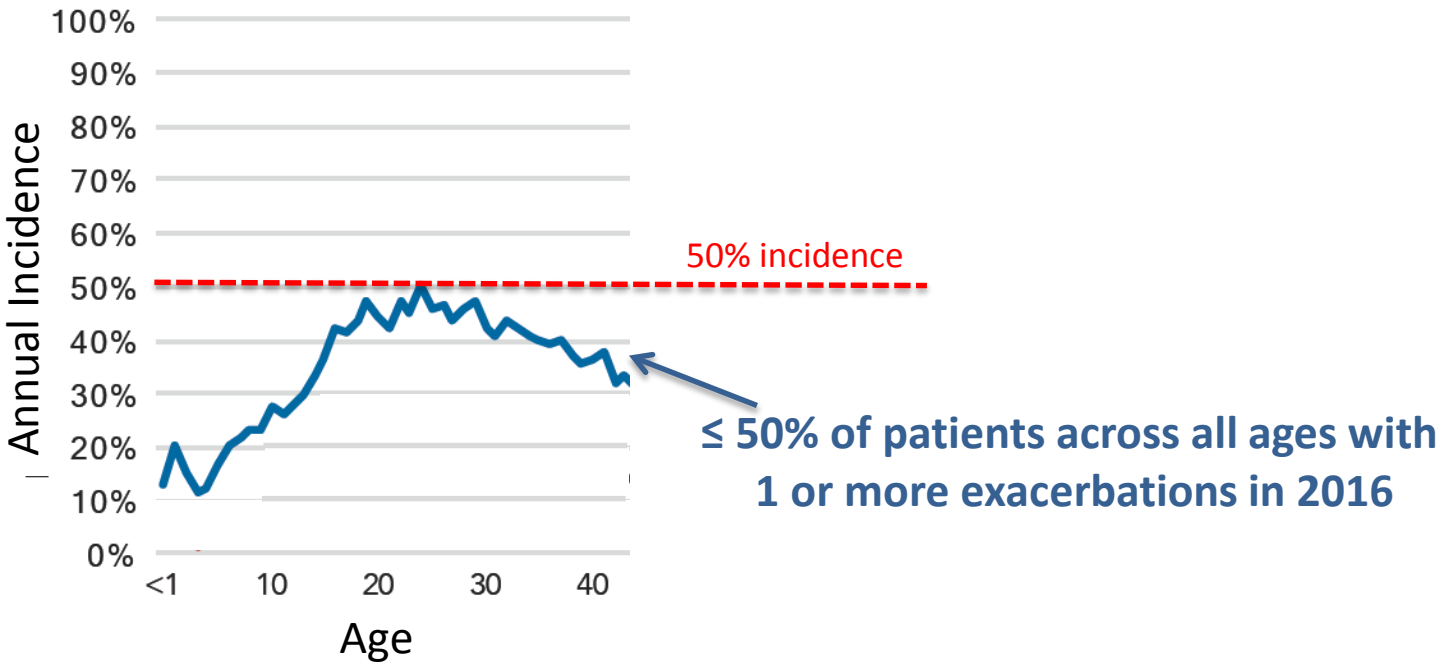
CFNPR 2016

steadily improving in target population (adults)

2016 median FEV_1% at upper limit of historic trial entry criteria (75%)

Historically, smaller FEV_1 effects in those with higher baseline FEV_1

Exacerbations as an alternative efficacy measure



Requires choice:

large study with low incidence vs. limiting eligibility to enrich

CFTR modulator drugs are improving baseline clinical status

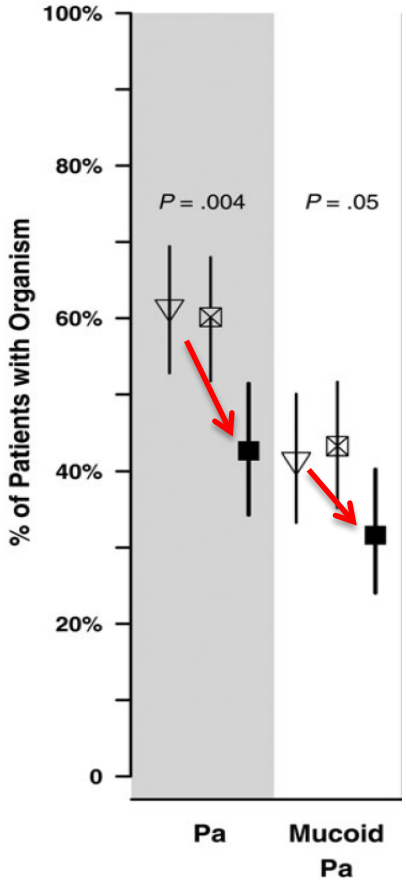
Clinical Trial Results Predict:

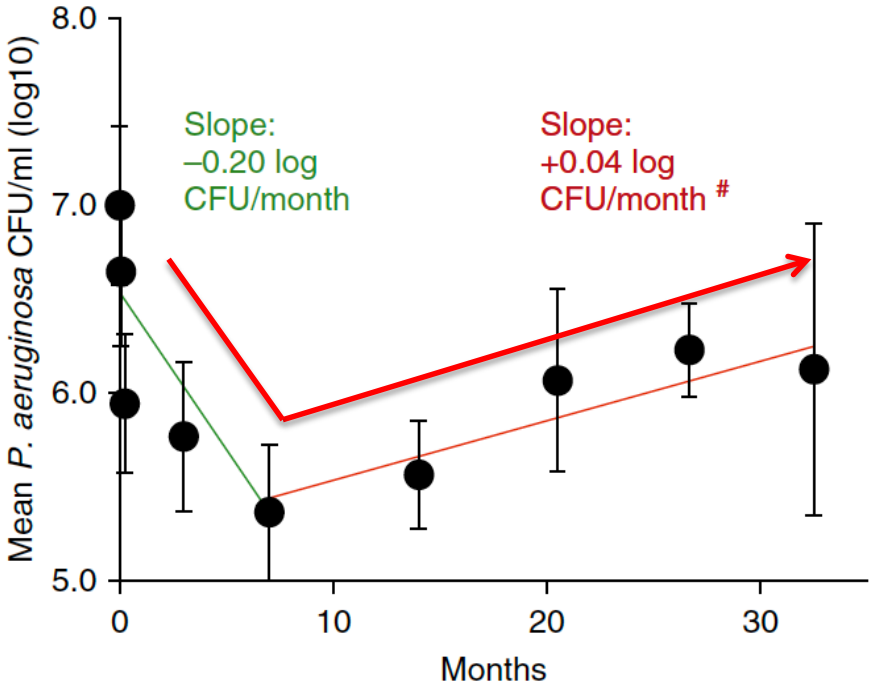
FEV_1%	↑ 10-15%
respiratory symptoms	↓ (large effect)
risk of exacerbation	↓ 50-65%

*applicable for ~95% of population by mutation
*uncertain durability and sub-group effects

J Cyst Fibros 2014; 13:29-36
PNAS 2009; 106; 44:18825-30
NEJM 2017; 377:21:2013-23
NEJM 2011; 365:18:1663-72
JCF 2018;17:83-88
AJRCCM 2014;15:175-84

CFTR modulator drugs are not eliminating the challenge of chronic *P. aeruginosa*





CID 2015. 60; 5:703-12

AJRCCM 2017. 195; 12:1617-28

Inhaled Antibiotics in CF

In view of persistent need and challenges, what data might be informative to the CF community and feasible to obtain?

1. strong pre-clinical data supporting rationale
   a. Antimicrobial effects, ideally in CF-relevant models and/or clinical isolates at achievable drug concentrations
   b. Drug characteristics indicating good candidate for inhaled use, maintaining excellent track record of safety
2. short placebo-controlled study with efficacy measures building upon class-effect
   a. Benefit to FEV_1 and/or patient reported outcomes (symptoms)
   b. Conduct in US or similar populations
3. longer duration open-label, active comparator study focused on safety and durability of effect
   a. Safety: toxicity, adverse events, risk of exacerbation
   b. Durability: FEV_1 over time, symptoms, risk of exacerbation

What about non-inferiority efficacy measures in the longer active comparator trials

-would clearly be helpful and could be assessed but notable limitations:

1. unblinded study design appears necessary

2. effect sizes hard to predict but may be more modest

   CAT use plus improving baseline health

3. We lack data on effectiveness of standard of care (i.e. CAT) needed to define the NI margins.

Summary

1. We need and are working to to develop new inhaled antimicrobial drugs in CF

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2. Improving health and practice patterns complicate feasible designs

    A. shorter placebo-controlled trials are possible in US
    B. Longer, unblinded ACT studies could be successful if carefully designed

Summary

1. We need and are working to to develop new inhaled antimicrobial drugs in CF

2. Improving health and practice patterns complicate feasible designs

    A. shorter placebo-controlled trials are possible in US
    B. Longer, unblinded ACT studies could be successful if carefully designed

3. Such data would be informative for CF providers

    A. shortcomings balanced by unmet needs
    B. much better than current data for off-label use
    C. preferable to more traditional studies in poorly-representative populations

Thank you

Assistance & feedback with slides:

Nicole Hamblet, PhD (TDN Coordinating Center, Seattle Children's Research Institute)
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Chris Goss, MD (TDN Coordinating Center, University of Washington)
Bonnie Ramsey, MD (TDN Coordinating Center, Seattle Children's University)
CF National Patient Registry Group, CF Foundation

Questions or Comments?