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
1. What’s happening now?
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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

Long-term clinical use (TOB) associates with improved survival (US CF Patient Registry 1996-2008)

Adjusted Survival Curves

Hazard Ratio=0.64 (P<.001)

<table>
<thead>
<tr>
<th></th>
<th>2-year mortality</th>
<th>5-year mortality</th>
<th>10-year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIS user</td>
<td>1.3%</td>
<td>5.2%</td>
<td>9.9%</td>
</tr>
<tr>
<td>TIS non-user</td>
<td>2.1%</td>
<td>8.0%</td>
<td>15.0%</td>
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Pediatr Pulmonol 2012; 47:44-52
Inhaled Antibiotics in CF

– Use patterns (in US)

2009 (N = 12,900)

- Aminoglycoside (94.7%)
- Colistimethate (16.4%)
- Aztreonam (3.7%)

2012 (N = 13,845)

- Aminoglycoside (83.9%)
- Colistimethate (12.3%)
- Aztreonam (40.3%)

2016 (N = 14,703)

- Aminoglycoside (83.4%)
- Colistimethate (12.9%)
- Aztreonam (43.2%)

2016 US CF National Patient Registry Data
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 (FEV₁ % ≤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
FEV₁% 25-75%
≥ 1 acute pulmonary exacerbation

Participated in RCT since 2010
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
1. What’s happening now?
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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.*
Ongoing appetite for new therapies from the CF community and industry sponsors.
Few Points Regarding Special Pathogens
increasing prevalence and no approved drugs

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>2001</th>
<th>2011</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin resistant <em>S. aureus</em> (MRSA)</td>
<td>7.3%</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Nontuberculous mycobacteria (NTM)</td>
<td>unknown</td>
<td>10.8%</td>
<td>12.7%</td>
</tr>
<tr>
<td><em>S. maltophilia</em></td>
<td>8.8%</td>
<td>14%</td>
<td>13.1%</td>
</tr>
</tbody>
</table>

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

- **YES**
  - *P. aeruginosa*
  - MDR *P.a.*

- **NO**
  - *S. aureus*
  - MRSA
  - *H. Influenza*
  - *S. maltophilia*
  - *Achromobacter*
  - *Bcc*

Percentage of Individuals

Year

CFNPR 2016
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.
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
1. What’s happening now?
   - current state of CF care and inhaled antibiotic use

2. What’s needed?
   - unmet need in inhaled antimicrobials

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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

![Diagram](image)

- **Run-in off Abx**
- **Safety Follow-up**
- **OFF**
- **Drug vs. Placebo**
- **ON or OFF**

Placebo: total period without therapy
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$_{1pp}$)

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$_1$% $\uparrow$ 10-15%

respiratory symptoms $\downarrow$ (large effect)

risk of exacerbation $\downarrow$ 50-65%

*applicable for ~95% of population by mutation
*uncertain durability and sub-group effects
CFTR modulator drugs are not eliminating the challenge of chronic *P. aeruginosa*
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 FEV₁ 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: FEV₁ 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 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 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:

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Bonnie Ramsey, MD (TDN Coordinating Center, Seattle Children’s University)

CF National Patient Registry Group, CF Foundation

Questions or Comments?