Challenges of Pharmacotherapy in the Treatment of Cystic Fibrosis

Hanna Phan, PharmD, BCPS
Clinical Assistant Professor, College of Pharmacy
Assistant Professor, College of Medicine
Clinical Pharmacy Specialist, Pediatric Pulmonary
Residency Program Director, Pediatric Pharmacy PGY2
August 30, 2011
Objectives

• **Name common medications** used in the outpatient and inpatient settings in the treatment of cystic fibrosis (CF)

• **Identify challenges** of treatment adherence in CF

• **Describe the role of a clinical pharmacist** as part of an interdisciplinary team in management of CF

**Conflict of Interest: I have no relevant financial relationships to disclose for this presentation.**
Disease Severity, Age, and Therapy

SA, 2 yo ♀
- CPT
- Creon 12,000
- Albuterol
- AquADEK liquid

EN, 7 yo ♀
- CPT
- Creon 12,000
- Albuterol
- Source CF
- Dornase alfa
- Tobramycin
- Fluticasone NS
- Budesonide

CM, 30 yo ♂
- CPT
- Creon 24,000
- Albuterol
- Source CF
- Dornase alfa
- Tobramycin
- Azithromycin
- Pantoprazole
- NaCl 7% Solution
- Dronabinol
- Megestrol
- Ursodiol
- Fluticasone NS
- Fluticasone/salmeterol
- Zolpidem

JS, 50 yo ♂
- CPT
- Ultrase MT 20
- Albuterol
- Source CF
- Vitamin D
- Dornase alfa
- Tobramycin
- Azithromycin
- Pantoprazole
- Insulin lispro
- Insulin lantus
- Clonazepam
- Fluticasone/salmeterol
- Hydrochlorothiazide
- Fluticasone NS
- Montelukast
- Docusate sodium

CPT = Chest physical therapy
CF Drug Therapy Basics

• Therapy selection depends on CF severity and organ systems affected
  – Pulmonary, infectious diseases, etc.
  – Gastrointestinal, hepatic, etc.

• Different pharmacokinetics with CF
  – Drug selection, dosing, frequency, adverse effects

• Off-label medication use

• ‘Polypharmacy’ is a common concern
Pharmacokinetic Challenges in CF

• Absorption
  – Differences in gastric pH
  – Slower GI motility

• Distribution
  – Larger volume of distribution

• Metabolism
  – Possible difference in hepatic clearance

• Elimination
  – Increased renal clearance
Overall Goals of Therapy

✔ Prolong survival

✔ Optimize/improve quality of life

✔ Slow disease progression

✔ Achieve normal growth and development

✔ Decrease hospitalization frequencies and duration

✔ Minimize adverse drug reactions
The CF Drug Development Pipeline

7/1/11
Pulmonary Drug Therapy
Bronchodilators – β agonists

- Nebulized or HFA inhaler
- Commonly used as part of CPT
  - Bronchial hyperresponsiveness, wheezing
  - Prevent bronchospasm during respiratory therapy and other inhaled treatments

- Albuterol
  - 2.5mg nebulized BID (w/ CPT), increased during exacerbation an/or hospitalization

- Levalbuterol
  - When to use versus albuterol?
  - Why is it not used for everyone?

Images, accessed 11/15/09:
http://peacehealthsleepcenter.org/kbase/media/medical/multum/proairhfa.jpg
http://www.healthsquare.com/common/images/d/DEY06971_86649_5.JPG
Dornase alfa (Pulmozyme®)¹,²

- Recombinant DNA enzyme
- Selectively cleaves extracellular DNA from pulmonary secretions, improve viscoelastic properties of secretions
  - Promotes airway clearance of mucous → reduce respiratory infection risk
  - ↓ Hospital LOS, duration of IV antibiotics
- Given as part of CPT regimen

Image, accessed 11/15/09:
Hypertonic Saline$^{1,3,4}$

- Increases hydration of airway surface liquid via osmotic flow
  - Breaks ionic bonds in mucus
  - Stimulates ciliary beat via the release of prostaglandin E2
  - Helps improve mucociliary clearance
  - Causes sputum production and cough → improve airway obstruction

- Should precede dose with bronchodilator (i.e., albuterol) to decrease incidence of bronchospasm, part of CPT

- 3% (3.5%) and 7% solutions
Corticosteroids

• **Inhaled**
  – Budesonide (Pulmicort®), Fluticasone (Flovent ®)
  – Attenuate reactive airways, reduce inflammation
  – Concurrent asthma

• **Systemic (oral)**
  – Prednisone
  – Reduce inflammation (?)
Quiz Break!

• Which of the following agents is currently available as an inhaler/MDI AND as a nebulizer?

A. Prednisone
B. Hypertonic saline
C. Dornase alfa
D. Albuterol
High-dose Ibuprofen\textsuperscript{1,5}

- Inhibits the migration, adherence, swelling, and aggregation of neutrophils, as well as the release of lysosomal enzymes
  - Decreases rate of decline of FEV1, decreases hospitalizations
  - Study population…

- Requires pharmacokinetic dosing

- ADE concerns: GI bleeding

- Currently not used in all patients
Azithromycin\textsuperscript{1,6}

- "Anti-inflammatory" agent
  - Immunomodulatory properties
  - Suppresses inflammation
  - Alters biofilm formation
- Not "antibiotic prophylaxis"
- Mon-Wed-Fri regimen
- Considerations
  - Check for presence of atypical mycobacterium
  - Patient weight
  - Presence of \textit{mucoid P. aeruginosa} and others...why?

Quiz Break!

• Which of the following agents is not commonly suggested as routine chronic maintenance drug therapy in CF?

A. Azithromycin
B. Dornase alfa
C. Ibuprofen
D. Prednisone
Antimicrobial Therapy\textsuperscript{7,8}

- **Intravenous (IV), oral (PO), or nebulized (NMT) route**
  - Treatment (mean duration ~ 14-21 days)
  - Prophylaxis (outpatient, on/off months)

- **Factors affecting antibiotic selection:**
  - Cultures and susceptibilities (past and present)
    - Often more than one pathogen…
  - Age
    - Child vs. adolescent vs. adult
  - Organ function (i.e., renal, hepatic)
  - History of allergies and adverse drug events

Antibiotics for CF Exacerbation\textsuperscript{7,8}

- Multi-drug resistant (MDR) pathogens are common

- 2+ drug therapy approach
  - From different drug classes
  - **Outpatient**
    - Oral agent(s) + nebulized agent + increased CPT
    - IV agent(s) ± oral agent(s) ± nebulized agent + increased CPT
  - **Inpatient**
    - IV agent(s) ± oral agent(s) ± nebulized agent + increased CPT
Commonly Used Antibiotics in CF: Oral Agents\textsuperscript{7,8}

- **S. aureus**
  - Methicillin-susceptible (MSSA)
    - Cephalexin, amoxicillin/clavulanate
  - Methicillin-resistant (MRSA)
    - Sulfamethoxazole/trimethoprim, clindamycin, linezolid

- **P. aeruginosa**
  - Ciprofloxacin

- **H. influenzae**
  - Amoxicillin/clavulanate, cefuroxime
Commonly Used Antibiotics in CF: Nebulized Agents \(^7,^8\)

- *P. aeruginosa*
  - Tobramycin (TOBI®)
  - Aztreonam (Cayston®)
  - Colistimethate (colistin)
Commonly Used Antibiotics in CF: IV Agents

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>Nafcillin (MSSA only)</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
</tr>
<tr>
<td></td>
<td>Clindamycin (watch for inducible resistance)</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Piperacillin / tazobactam</td>
</tr>
<tr>
<td></td>
<td>Cefepime</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
</tr>
<tr>
<td></td>
<td>An aminoglycoside - tobramycin or amikacin</td>
</tr>
</tbody>
</table>
Commonly Used Antibiotics in CF: IV Agents\textsuperscript{7,8}

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. maltophilia</em></td>
<td>Sulfamethoxazole / trimethoprim</td>
</tr>
<tr>
<td></td>
<td>Piperacillin / tazobactam</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin or moxifloxacin</td>
</tr>
<tr>
<td></td>
<td>Ticarcillin / Clavulanate + aztreonam</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>All drugs listed for P. aeruginosa provide coverage (rec. 3\textsuperscript{rd} gen cephalosporin), may not need for double coverage combination</td>
</tr>
</tbody>
</table>
Commonly Used Antibiotics in CF: IV Agents\textsuperscript{7,8}

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{B. cepacia}</td>
<td>Sulfamethoxazole / trimethoprim, meropenem, or ciprofloxacin, may need multiple drug combination; known to be resistant to AGs</td>
</tr>
<tr>
<td>\textit{Nocardia}</td>
<td>Sulfamethoxazole / trimethoprim, minocycline, or linezolid, multiple drug combinations usually not necessary</td>
</tr>
</tbody>
</table>
## Antifungal Agents

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antifungal</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida spp.</em> (most)</td>
<td>Fluconazole</td>
</tr>
<tr>
<td><em>Aspergillus spp.</em></td>
<td>Itraconazole</td>
</tr>
<tr>
<td><em>Scedosporium apiospermum</em></td>
<td>Voriconazole</td>
</tr>
</tbody>
</table>
Antibiotic Prophylaxis$^{1,11}$

- Some patients may be given oral antibiotic therapy for prophylaxis (rare)

- **Most common form is nebulized antibiotics**
  - Tobramycin solution (TOBI®)
  - Colistimethate (colistin)

- The above are given twice a day, 28 days on/off schedule
Quiz Break!

Which of the following pathogens do we starting using inhaled TOBI for?

A. *H. influenzae*
B. *Aspergillus* spp.
C. *P. aeruginosa*
D. *S. aureus*
CFTR Mutation...Treatment?

• **Class III:** Defective regulation of CFTR even though it is able to reach the apical cell surface
  – *Example: G551D*
CFTR Modulators

• **VX-770** – oral agent (150mg BID)
  – Potentiator, acts on non-functional, properly localized CFTR
  – Patient must have one copy of G551D
  – Improvements in nasal potential difference, sweat chloride measurements
  – Improved FEV1, weight gain, decreased pulmonary exacerbations, symptoms
  – Adverse drug effects similar to placebo
  – FDA NDA in process….
CFTR Mutation…Treatment?

- **Class II: Defective trafficking of CFTR, thus does not reach the apical surface membrane where it can function**
  - *Example:* ΔF508del
CFTR Modulators

- **VX-809** – oral agent (200mg BID)
  - *Corrector*, acts to move defective CFTR to the right location, improve function as Cl-channel
  - Studied alone in patients with ΔF508del → improved sweat chloride, no change FEV1

- **VX-809 + VX-770**
  - VX-770 potentiates VX-809
  - Phase 2 trials in patients with ΔF508del
CFTR Mutation...Treatment?

- **Class I:** Defective protein production with premature termination of CFTR production; produce few or no functioning CFTR chloride channels
  - “nonsense mutations”
CFTR Modulators

- **Ataluren (aka. PTC124)** – oral agent (40mg/kg (?) TID)
  - Promoter, help produce functioning CFTR chloride channels
  - Patients with nonsense mutations
  - Currently in starting phase 3 trials…
Quiz Break!

• Which of the following agents is pending FDA approval soonest based on current data?

A. VX-770
B. VX-809
C. VX-770 + VX-809 combination
D. Ataluren (PT124)
Gastrointestinal and Nutritional Drug Therapy
Concurrent GI/Nutrition Issues

- Malabsorption (pancreatic insufficiency)
- Gastroesophageal reflux disease (GERD)
- Poor intake/appetite
- Gastroparesis
- Hepatobiliary disease
- Distal intestinal obstruction syndrome (DIOS)
- CF related diabetes (CFRD)
Pancreatic Insufficiency\textsuperscript{12,13}

- Pancreatic enzyme replacement therapy (PERT)
- Several manufacturers – Creon®, Pancrease®, Pancrearb®, Ultrase®, Viokase®, ZenPep®, Pangestyme™
- FDA Ruling – All manufacturers of pancreatic enzyme products must secure FDA approval of their products by submitting New Drug Application by 4/2009 in order to remain available to patients
<table>
<thead>
<tr>
<th>Brand</th>
<th>Lipase</th>
<th>Protease</th>
<th>Amylase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon ®</td>
<td>6,000</td>
<td>19,000</td>
<td>30,000</td>
<td>G-tube admin</td>
</tr>
<tr>
<td></td>
<td>12,000</td>
<td>38,000</td>
<td>60,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24,000</td>
<td>76,000</td>
<td>120,000</td>
<td></td>
</tr>
<tr>
<td>Zenpep®</td>
<td>5,000</td>
<td>17,000</td>
<td>27,000</td>
<td>G-tube admin</td>
</tr>
<tr>
<td></td>
<td>10,000</td>
<td>34,000</td>
<td>55,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15,000</td>
<td>51,000</td>
<td>82,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20,000</td>
<td>68,000</td>
<td>109,000</td>
<td></td>
</tr>
<tr>
<td>Pancreaze®</td>
<td>4,200</td>
<td>10,000</td>
<td>17,500</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10,500</td>
<td>25,000</td>
<td>43,750</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16,800</td>
<td>40,000</td>
<td>70,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21,000</td>
<td>37,000</td>
<td>61,000</td>
<td></td>
</tr>
</tbody>
</table>
Pancreatic Insufficiency

- **Nutritional supplements**
  - **Fat-soluble vitamins**
    - Vitamins A, D, E, and K
      - ADEK®, AquADEK®, SourceCF®
    - Vitamin D
      - Ergocalciferol (D2), Cholecalciferol (D3)
    - Vitamin E
      - Over the counter supplement formulations (capsules)
  - **Iron supplements**
    - Ferrous sulfate, ferrous gluconate
    - Considerations with GERD medications…
Gastroesophageal reflux disease (GERD)$^{15,16}$

- > 25-30% incidence
- Histamine-2 receptor antagonists (H2RA)
  - Famotidine
  - Ranitididine
- Proton pump inhibitors (PPI)
  - Pantoprazole, lansoprazole, omeprazole, esomeprazole
  - “Enzyme Boosting”

Images, accessed 11/29/09:
http://i45.photobucket.com/albums/f77/pharmerpillid/Prevacid15mgODT.jpg
http://myhealth.ucsd.edu/library/healthguide/en-us/images/media/medical/Multum/protonix40mg.jpg
Quiz Break!

• Which of the following agents is there data for use for pancreatic enzyme “boosting”

A. Azithromycin  
B. Ergocalciferol  
C. Famotidine  
D. Lansoprazole
Poor Appetite\textsuperscript{19}

- **CF anorexia** due to:
  - Elevated serum cytokines due to chronic infection
  - Smell/taste disturbance due to sinusitis
  - GERD
  - Aggressive nutritional interventions
  - Behavioral/psychosocial factors

- Not all CF patients will require drug therapy, but continued nutritional failure leads to considered added drug therapy
Poor Appetite: Appetite Stimulants

- **Megesterol**
  - Synthetic progestin with antiestrogenic effects
  - Cytokine inhibition

- **Cyproheptadine**
  - Histamine and serotonin antagonist
  - Side effect of appetite stimulation

- **Dronabinol**
  - Psychoactive substance, side effect of appetite stimulation

- **Mirtazapine**
  - Antidepressant, side effect of appetite stimulation and weight gain
Gastroparesis$^{17,18}$

- Often related to CFRD
- Affects the ability of the stomach to empty its contents
- Drug therapy that helps nausea/vomiting
  - Ondansetron (Zofran®)
  - Prochlorperazine (Compazine®)
- Drug therapy can help increase motility
  - Metoclopramide (Reglan®)
  - Erythromycin (E-Mycin®)
Hepatobiliary Disease

• Up to 30% incidence, usually later in life
• Bile duct obstruction from abnormal bile composition and flow (cholestasis)
• Potential complications:
  – Cirrhosis
  – Biliary colic secondary to cholelithiasis
  – Portal hypertension $\rightarrow$ liver transplant
Hepatobiliary Disease\textsuperscript{19,20}

- **Drug therapy:** Ursodiol
  - Ursodeoxycholic acid

- **Clinical effects**
  - Slows progression of disease, improves bile flow
  - Displaces toxic bile acids and reduces liver enzymes
  - Stimulates bicarbonate and chloride secretion

Distal intestinal obstruction syndrome (DIOS)

- Obstruction of the right colon and/or terminal ileum with viscid fecal matter
- Presentation: colicky periumbilical and/or right lower quadrant pain, abdominal distension, nausea/vomiting, decreased stool output
- Risk factors:
  - PERT non-adherence, dehydration, narcotic use
Distal intestinal obstruction syndrome (DIOS)

- **Treatment**
  - Hydration
  - Use of drug therapy
    - Polyethylene glycol (Miralax®, GoLytely®)
    - Enemas
    - N-acetylcysteine
  - Surgical resection
AK is a 7 year old whose pancreatic enzymes are appropriately dosed (and adherent) and currently on lansoprazole. Her Mom states that she just doesn’t want to eat despite her best efforts in motivating her…what is an appropriate drug therapy to consider?

A. Ursodiol
B. Raniditine
C. Metoclopramide
D. Cyproheptadine
CF-Related Diabetes (CFRD)²⁰

- Not really Type I or 2 diabetes mellitus…
- Insulin vs. oral agents
  - Standard = Insulin (e.g. insulin glargine (long-acting) + lispro (intermittent short-acting)) + carbohydrate counting
  - Oral agents not recommended, but occasionally used
    - Evidence demonstrating efficacy lacking
- Possible affects of drug therapy on serum glucose levels
Other Concurrent Drug Therapy

• Pediatric
  – Psychiatric disorders
    • Attention deficit hyperactivity disorder (ADHD)
    • Major depressive disorder
  – Seizure disorder

• Adult
  – Psychiatric disorders
    • Bipolar disorder
    • Major depressive disorder
  – Hypertension
  – Hyperlipidemia
CF Interdisciplinary Team

✓ Physician
✓ Clinical Pharmacist
✓ Nurse Clinician
✓ Clinical Dietitian
✓ Respiratory Therapist
✓ Social Worker
✓ Health Care Trainees (e.g. MSW, MD, RT, PharmD)
Role of the Clinical Pharmacist

✓ Educate other health care professionals about therapy options based on the most recent biomedical literature.

✓ Patient/caregiver education regarding mediation use, safety, and efficacy.

✓ Recommend and monitor CF regimens (i.e., kinetics, medication review)

✓ Serve as a clinical researcher in evaluating effective and safe treatment options for children, adolescents, and adults with CF.
My Pathway to Pediatric Pulmonary Medicine…

**Undergraduate studies**  
(The University of Michigan)  
4 years

**Clinical Practice**  
(Pediatrics, NICU)  
3 years

**Doctor of Pharmacy (PharmD)**  
(The University of Michigan)  
4 years

**Postdoctoral Fellowship**  
(The Ohio State University, The Research Institute at Nationwide Children’s Hospital)  
2 years

**Clinical Assistant Professor and Clinical Pharmacy Specialist**  
(The University of Arizona, College of Pharmacy)

Continued scholarship, practice, and teaching in pediatric pharmacotherapy with focus in pulmonary medicine
<table>
<thead>
<tr>
<th>CF Clinic</th>
<th>Inpatient</th>
<th>Scholarship and Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Intake and assessment of medication regimens</td>
<td>• Notified of new admissions to UMC</td>
<td>• Participate in research in the ARC</td>
</tr>
<tr>
<td>• Assessment of adherence</td>
<td>• Evaluate and assess patient data (e.g., cultures) and recommend initial antimicrobial regimen and lab monitoring parameters</td>
<td>• Asthma</td>
</tr>
<tr>
<td>• Recommend drug therapy for maintenance and exacerbations</td>
<td>• Weekly rounding with team to assess progress and recommend any changes in therapy</td>
<td>• CF</td>
</tr>
<tr>
<td>• Education</td>
<td></td>
<td>• Participate in the education of health care professional trainees</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fellows</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Residents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Students</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• PPC trainees</td>
</tr>
</tbody>
</table>
Summary

• CF drug therapy is multi-faceted, often involving multiple organ systems with use of various dosage forms.

• Drug dosing in CF may differ from non-CF due to differences in pharmacokinetics and pharmacodynamics, although much is still unknown.

• Interdisciplinary approach to drug therapy selection and patient education is essential to optimize outcome
Questions?

hphan@pharmacy.arizona.edu
References


