Management of Respiratory Failure in CF and Bronchiectasis

Joseph M. Pilewski, M.D.
University of Pittsburgh
University of Pittsburgh Medical Center
Children’s Hospital of Pittsburgh of UPMC
Improved Survival with Treatment Innovation

Advances in therapy have been incremental
- Individual benefit is modest but cumulative
- Life expectancy greatly increased

1st pathologic description
1st successful pregnancy
Sweat chloride test developed
Discovery of high salt in sweat
Airways Clearance
Neonatal screening
NPD and Cl transport
CF gene identified
Azithromycin
HTS
AZLI
Inhaled colistin
Inhaled Tobramycin
rhDNase
Antipseudomonal antibiotics
Antistaphylococcal antibiotics
Airway clearance
Pancreatic Enzymes

Stratified/Precision Medicine for CF

Mist tents
Center care
Ivacaftor
Colobreathe
Bronchitol
TIP


Age (years)

Courtesy Professor Stuart Elborn
Overview

• Respiratory failure in Cystic Fibrosis
• Treatment options
  – Non-invasive ventilation (NIV)
  – Invasive mechanical ventilation (MV)
  – Extracorporeal membrane oxygenation (ECMO)
  – Lung transplantation
Pathophysiology and treatments for CF

- **CFTR gene defect**
  - Abnormal CFTR protein
  - Defective ion transport
  - Airway surface liquid depletion
  - Delayed mucociliary clearance

- **Infection**
  - Mucus Obstruction
  - Lung transplantation

- **Inflammation**
  - End Stage Lung Disease

- **Exercise/clearance/DNase**
  - Antifungal
  - Antiviral

- **ENaC inhibitors**
  - Mannitol

- **Hypertonic saline, Mannitol**

- **CFTR modulators**
  - VX-661/ lumacaftor / Ivacaftor / QBW251
  - Parion P-1037

- **CF gene therapy/editing**

**Treatment Options**
- Antibiotics
- ENaC inhibitors
- CFTR modulators
- CF gene therapy/editing
- Parion P-1037

Additional Resources:
- http://www.cftr2.org/
- CF gene therapy/editing
Mechanisms of respiratory failure in CF

Airway infection, inflammation, mucus plugging

Airway obstruction and bronchiectasis

V/Q mismatch/ DLCO

hypoxemia

Pulmonary hypertension

SvO2

Cor pulmonale

Vital capacity

dead space

Increased work of breathing/muscle fatigue

Alveolar hypoventilation

hypercapnea

Adapted from Yankaskas
Time course of respiratory failure and impact on outcome

- Acute, typically due to exacerbation/ABPA, hemoptysis, pneumothorax, pulmonary edema, pulmonary embolism or extrathoracic surgery
- Chronic, due to gradually progressive obstructive lung disease
- Acute on chronic, typically precipitated by exacerbation, pneumothorax, hemoptysis
Bronchial artery embolization for hemoptysis

- Initial control of hemoptysis in 75% with one embolization session, 89% with two, 93% with three (UNC experience)
- Recurrent episodes often due to non-bronchial systemic collaterals
- Complications: chest pain, embolization of other vessels (spinal arteries)

Bronchopleural fistula in end stage CF
Chronic hypercapnic respiratory failure

- 37 yo woman; late diagnosis of CF after presented with bronchiectasis and atypical mycobacterial infections; prior right upper lobectomy for *M. avium*
- Progressive obstructive lung disease, FEV₁ 0.7 (26% pred), FVC 1.0 (30% pred); 6 Minute walk 695 feet
- No headaches or daytime somnolence
- pH 7.42, pCO₂ 53, pO₂ 49 on room air
Treatment options

• Pulmonary rehabilitation
• End of life discussion
• Oxygen alone: blunt hypoxemia, prevent PAH
• Non-invasive ventilation (NIV) to
  – Blunt hypoventilation by increase $V_E$
  – Reduce work of breathing
    • Nasal Bilevel Positive Airway Pressure (BiPAP)
    • Face mask BiPAP
    • Negative pressure device
Summary of NIV for chronic hypercapnic respiratory failure in CF

• Acclimatization in sleep lab (or hospital)
• Nasal mask preferred over face mask
• Evidence for favorable effects on oxygenation and hypercapnea, chest symptoms, exercise capacity, and nutritional status (Moran et al., 2009)
• Other indications: blunt oxygen desaturation during awake airway clearance (Fauroux 1999, Kofler 1998)
• Useful ‘bridge’ to transplantation, and improves priority on waiting list (Lung Allocation Score)
Refractory hypercapnic respiratory failure

- 30 yo with progressive obstructive lung disease, oxygen dependent for 6 years, admitted with dyspnea
- MDR *Pseudomonas aeruginosa*, *Achromobacter xylosoxidans*, *Scedosporium apiospermum*
- Dyspneic, mild frontal headache
- Initiated NIV with IPAP 16/EPAP 6
- pH 7.35, pCO$_2$ 86 on 6 L/min nasal oxygen
- 14 d later, worsening lethargy/headaches;
  
  pH 7.12, pCO$_2$ >114
Options

- Continue non-invasive mechanical ventilation
- Intubate for mechanical ventilation

Implications for physiologic goals:

- **airway clearance** – MV reduces cough clearance; oscillating bed, CPT/PD, VEST, bronchoscopy
- **increase alveolar ventilation** – airway resistance, air trapping, and high dead space
- **Unload and rest respiratory muscles**
Ventilator parameters

• Mode:
  – pressure cycled (Pressure Support or Pressure assist Ventilation, PC, Bi-level)
  – volume cycled (PRVC)

• Minute ventilation goal: correct acidemia
  – low TV (6 ml/kg) to minimize airway pressures
  – higher TV (8-10 mg/kg) to minimize dead space to tidal volume ratio and allow prolonged expiratory time to minimize air trapping
• Inspiratory pressure parameters:
  – minimize barotrauma and plateau pressures
  – peak pressures difficult to manage: set flow rate or inspiratory time to increase ET
  – Intrinsic PEEP is common due to air trapping
  – Apply low level extrinsic PEEP to minimize airway closure during expiration
• Low flow or pressure trigger
• Reduce dead space in ventilator tubing
• Avoid paralytics
• Liberal sedation with propofol or fentanyl/benzodiazepene
Supportive therapies

• Bronchodilators, pulmozyme and hypertonic saline

• Antibiotics; consider continuous infusion β-lactam (Hayes et al., *Lung* 2011)

• Consider trial of systemic steroids - ~ 1-2 mg/kg/day methylprednisolone for 2-3 days

• Inhaled steroid to minimize airway edema

• Nebulized N-acetyl cysteine as mucolytic

• Initiate post-pyloric enteral feeding immediately

• Maintain serum bicarbonate
Failure to wean

• Causes:
  – uncontrolled infection and high CO$_2$ production
  – Mucus plugging and air trapping
  – malnutrition/hypophosphatemia/acidemia
  – anxiety

• Benefits of early tracheostomy
  – Minimize sedation
  – Promote mobilization and minimize deconditioning
  – Reduce dead space
  – Facilitate secretion clearance
Lung transplantation for end stage CF on mechanical ventilatory support

- Historically suboptimal outcomes from ventilator
- Pre-LAS study for CF: Wisconsin and UNC
  - 8 CF patients on MV (3-153 days) at time of transplant to 24 'typical' CF patients
  - Time to extubation: 11 vs 4 days; CBP 88 vs 29%
  - 1 year FEV1: 86 vs 90% predicted

Bartz et al., *JHLT* 2003
ECMO as bridge to lung transplant

- Anecdotal reports of short term ECMO prior to lung transplant
  - Veno-venous
  - Veno-arterial with cannulation of femoral vein and aorta

Median follow-up 2.3 years; 4 CF, 6 pulmonary fibrosis, 6 re-transplant (Bermudez et al., *Ann Thor Surg* 2011)
Evolution to ‘ambulatory’ ECMO

- Series of 4 patients with CF
- Hypercapnea, pCO$_2$ 97-137 on MV
- ECMO 2-15 days prior to transplant
- LOS 15-28 days

Hayes et al., *J Cystic Fibrosis* 2012
Conventional vs ambulatory ECMO

Conventional

6 d VV ECMO; LOS 33 d

Ambulatory

20 d VV ECMO; LOS 27 d
Summary

• Non-invasive and invasive ventilatory support benefits some patients with chronic respiratory failure
• Prognosis is very poor in patients who progress to MV in hospital in spite of aggressive medical therapy
• Acceptable outcomes in majority of patients on MV as bridge to transplant; early ECMO promising option
• Need clinical studies – prospective trials of early NIV and ambulatory ECMO; studies of invasive MV