

## **Neonatal/Pediatric Cardiopulmonary Disease**

### **SIDS, Cystic Fibrosis**

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## **Sudden Infant Death Syndrome (SIDS)**

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## **Review**

- Apnea
  - Cessation of respiratory airflow
  - Central
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  - Obstructive
    -
- Mixed

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## Review

- Apnea
  - Not all pauses are abnormal
  - Abnormal if cyanosis, bradycardia, or >20 sec.
  - Abnormal apnea is a clinical sign of some underlying pathology & not a final diagnosis

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## SIDS

- Is a Dx made post mortem whenever a previously healthy infant dies suddenly & unexpectedly during sleep **and**
- Autopsy cannot reveal an adequate explanation
- Vast majority of infants dying from SIDS have no Hx of apnea

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## SIDS

- Crib Death
- Worldwide problem (in western nations = leading cause of death in ages )
- 2/1000 live births
- No cause has been established although are many theories
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### Patterns

- Maternal characteristics
- Infant characteristics at birth
- Infant characteristics near time of death

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### Maternal Characteristics

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- Black, Native American or Alaskan
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- Smokes cigarettes (major factor, includes passive smoke)
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- Ill during
- Inadequate

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### Infant Characteristics (at Birth)

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- Low
- Resuscitated with
- 2<sup>nd</sup> or 3<sup>rd</sup> in birth or of multiple pregnancy
- Previous siblings who

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**Infant Characteristics  
(Near Death)**

- Age
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- Mild illness in
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“Classic” victim is a premature black male infant born to a poor, young mother who did not receive prenatal care. Death occurred between 1-3 mo., in the winter, while the infant was sleeping at night.

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- No evidence that SIDS is genetic although does seem to be increased risk in survivor of twins
- Have been several reported cases of families with 3 or more SIDS deaths but in all circumstances, it was determined that cause of death was asphyxia (child abuse)

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### Post-Mortem Pathology

- No uniform data
- ~ 2/3
  - Hyperplasia of brainstem astroglia & smooth muscle in pulm arteries which suggests that hypoxia or ischemia occurred for long periods before death
  - Mild inflammation of resp tract
  - Intrathoracic petechiae

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### Post-Mortem Pathology

- No histological data suggests deaths from cardiac dysrhythmia
- No differences found in serum or tissue chemistries when compared to infants who died of known causes
- Negative analysis for toxins or drugs

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- Since final common event is cessation of breathing, much interest has focused on whether the previously healthy SIDS victims have had asymptomatic mild, abnormal control of respiration before death

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### Respiratory Control

- Highly complex involving CNS integration of afferent neural signals from peripheral receptors which sense physical & chemical changes in the body
- Signals are followed by coordination of respiratory muscle activity

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### Respiratory Control

- Proper function of this respiratory control system is altered by
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- Impossible to prove since don't know SIDS victims ahead of time

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### Approaches to Study #1

- Studied the ventilatory responses to hypoxia & hypercapnia in siblings & parents of SIDS victims
- ⇓
- Did not identify any consistent abnormalities that would warrant testing of families or infants to identify future victims

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## Approaches to Study #2

- In England - performed 24-hour recordings of RR & HR on 6914 full-term infants & 2337 premature & low birth weight infants  
↓
- 27 later died from SIDS - review of recordings showed no prolonged apnea or bradycardia  
↓
- Computer-assisted analysis of all 9251 recordings have shown that 2 SIDS victims had an abnormally high incidence of short apnea + 2 SIDS victims had an abnormal incidence of tachycardia  
↓
- 23 of the 27 SIDS victims had *no* abnormalities

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## Approaches to Study #3

- Other studies have looked at cardiorespiratory control of infants who have suffered an ALTE  
(*Apparent Life-Threatening Experience = experience that is frightening to the observer & is characterized by some combination of apnea, cyanosis, pallor or marked change in muscle tone, usually limpness - observer usually reports that if he/she had not intervened, the infant would have died*)  
↓
- Problem with studying these infants is that not all of them are “near-miss” SIDS  
↓
- Not surprising - no consistent abnormalities of cardiorespiratory control have been identified

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## Current Theories

- Botulism poisoning ruled out
- Prolonged Q-T interval
- Increased levels of interleukin-6 in CSF
- Surfactant abnormalities
- GE reflux
- Abnormal pulmonary inflammatory response
- Maternal cocaine use
- Basement membrane thickening of vocal cords

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## Conclusions

- So where are we??
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- In the meantime -----

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- Victims families need help to cope with grief, shock, anger, guilt, anxiety
  - Support group are located t/o USA

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- Most centers prescribe immediate, continual monitoring for surviving twin, triplets, etc.
  - HR, RR, SpO<sub>2</sub>
  - Apnea monitoring (impedance pneumography) which has not been shown to ↓ incidence
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    -
  - Polysomnography (in hospital)

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- Nation-wide campaign “Back to Sleep” **has** reduced incidence of SIDS but we are now seeing mal-shaped heads as a result of always sleeping on the back

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## Cystic Fibrosis

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## CF

- = hereditary disease affecting all exocrine glands (esp. GI tract & lungs) causing thick, copious secretions
- Defect in a single gene on chromosome 7
  - 70% of all CF patients have this defect of a triplet nucleotide deletion at the 508<sup>th</sup> amino acid =
  - Over 100 mutations, ex. R117H
  - Any mutation = “a bad copy” of the good gene

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## CF

- Majority of CF cases get a bad copy from Mom & 1 from Dad (not necessarily the same defect)
- Recessive gene
  - Both parents must be carriers (4% of all people)
  - Each pregnancy carries 25% chance of CF

|   |    |    |
|---|----|----|
|   | C  | f  |
| C | CC | Cf |
| f | Cf | ff |

|   |    |    |
|---|----|----|
|   | f  | f  |
| C | Cf | Cf |
| f | ff | ff |

|   |    |    |
|---|----|----|
|   | f  | f  |
| C | Cf | Cf |
| C | Cf | Cf |

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## CF

- Unfortunately, even having one “bad copy”, while not full-blown CF, can cause “CF-like” problems

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## CF

- The “good gene” gene encodes a membrane protein called cystic fibrosis transmembrane conductance regulator (CFTR)
  - CFTR regulates the flow of ions (sodium, chloride) through exocrine glands → unable to regulate the salt composition of secretions → insufficient secretion of fluid & inadequate hydration → thickened secretions of pancreas, lungs, liver, gallbladder, reproductive organs, sweat glands

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## CF

- Males = females
- 1/1500-2000 births
- Most common life-threatening chronic pulmonary disease in children
- Problems have been somewhat minimized due to
  - Increased knowledge of intestinal problems
  - Availability of pancreatic enzymes
  - Vitamin supplements
  - Low-fat diets

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## CF

- Greatest threat to life is
  - Progressive pulmonary involvement
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## Medical History

- "Failure to thrive"
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- Recurrent pulmonary infections
- Recurrent sinusitis
- Development of nasal polyps
- Sterility
  - Women-
  - Men-

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### Sign & Symptoms

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### Sign & Symptoms

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- Late disease -
- ABGs
  - Early disease -
- Late disease -

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### Sign & Symptoms

- CXR
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- PFT
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## MB

- MB is a 6 yof who was brought to the pulmonary clinic by her parents for the first time with complaints of dyspnea and a productive cough. She has had a productive cough for a couple of years and periodically developed yellow or green sputum and occasional hemoptysis. These symptoms were attributed to bronchiectasis, and her parents were told she had asthma as well. She also has had several respiratory infections requiring hospitalization. Her home therapy includes inhaled albuterol and occasional antibiotic therapy. She has had no regular pulmonary hygiene program.

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## MB

- Three weeks before admission she developed increasing cough producing greenish sputum. Her parents have also noticed increasing dyspnea and wheezing. Her family physician gave her a prescription for ciprofloxacin 500 mg BID but her symptoms progressed despite this therapy. This was the 3rd such episode MB has experienced in the last year. Her previous episodes were successfully treated with oral ciprofloxacin. She has also had difficulty maintaining weight and is below her ideal weight. She did have fever, chills, pharyngitis, purulent nasal discharge. She has had no problems with steatorrhea, nasal polyps, or sinus infections.

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## MB

- MB's parents do not smoke. She has a younger sister who has CF and an older brother who is healthy. Her father has a chronic problem with bronchiectasis that began as a teenager. MB has been tested for CF using a sweat chloride concentration when she was first diagnosed with bronchiectasis. Her sweat chloride concentration was 57 mEq/liter.
- What features of this patient's history support the diagnosis of cystic fibrosis?

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### MB

- Which parts of MB's history suggest that she does not have CF?
- Does her sweat chloride concentration help to clarify whether or not she has CF?

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### MB

- What findings would you expect to find on physical exam if this patient has CF?
- What additional testing would be appropriate to support or refute the diagnosis of CF?

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### MB Physical Exam

**General** A thin, young child with a productive cough; uses accessory muscles of respiration but appears to be breathing comfortably and can converse w/o apparent distress.

**Vital** Temp 37.2°C (99°F)

**Signs** HR 105/min

RR 24/min

BP 90/46

**HEENT** Nasal polyp seen in left nares; no sinus tenderness noted; oral exam normal and mucous membranes moist; eye and ear exam normal

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## MB Physical Exam

**Neck** Trachea midline; both carotid impulses normal in contour and intensity; no jugular vein distention

**Chest** AP diameter of chest increased; diffuse inspiratory and expiratory crackles with polyphonic expiratory wheezing heard over both lungs; hyper-resonance noted with percussion

**Heart** Regular rate with loud P<sub>2</sub> component of 2<sup>nd</sup> heart sound noted on auscultation; no murmurs or gallops noted; PMI difficult to appreciate but located in the 5<sup>th</sup> intercostal space 2-3 cm lateral to sternal border

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## MB Physical Exam

**Abdomen** Bowel sounds active, with no guarding or tenderness; liver 5 cm wide in the midclavicular line; no masses palpated

**Extremities** Digital clubbing but no cyanosis or edema; pulses equal and symmetric

- This patient does not have a fever at the time of exam or a history of fever before this visit. Does the lack of fever indicate the patient does not have a significant exacerbation of her lung disease?

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## MB

- What is the significance of this patient's underweight appearance?
- What is a nasal polyp, and what respiratory problems may it create?
- What is indicated by an increase in the AP diameter of the chest?

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### MB

- What is the significance of the crackles heard over the lungs?
- The 2<sup>nd</sup> heart sound has 2 components, an aortic ( $A_2$ ) and a pulmonic ( $P_2$ ) sound. Describe the source of these heart sounds and the meaning of a loud  $P_2$ .

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### MB

- Why does the patient have a cardiac PMI that is decreased in intensity and displaced from the normal position?
- Describe what clubbing of the fingers looks like and what it may indicate.
- What laboratory work should be ordered at this time?

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### MB Lab Results - ABGs

Room air  
 pH 7.42  
 PaCO<sub>2</sub> 34 mmHg  
 PaO<sub>2</sub> 67 mmHg  
 Bicarb 21 mEq  
 P(A-a)O<sub>2</sub> 39 mmHg  
 O<sub>2</sub> 17.5 vol%  
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### MB Lab Results - CBC

|                      |        |                      |
|----------------------|--------|----------------------|
| WBC                  | 12,400 | 4,000-11,00/ $\mu$ L |
| RBC                  | 4.7    | 4.1-5.5 M/mL         |
| Hgb                  | 14.2   | 12-16.5 g/dL         |
| Hct                  | 43     | 37-50%               |
| <i>Differential:</i> |        |                      |
| Segs                 | 72%    | 38-79%               |
| Bands                | 12%    | 0-7%                 |
| Lymphocytes          | 13%    | 12-51%               |
| Monocytes            | 1%     | 0-10%                |
| Eosinophils          | 1%     | 0-8%                 |
| Basophils            | 1%     | 0-2%                 |

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### MB Lab Results - Chemistry

|                 |     |                |
|-----------------|-----|----------------|
| Na <sup>+</sup> | 138 | 136-146 mEq/L  |
| K <sup>+</sup>  | 4.6 | 3.5-5.1 mEq/L  |
| Cl <sup>-</sup> | 106 | 90-110 mEq/L   |
| Bicarb          | 20  | 22-29 mEq/L    |
| BUN             | 13  | 7-18 mg/dL     |
| Creatinine      | 0.5 | 0.3-0.7 mg/dL  |
| Calcium         | 8.8 | 8.8-10.8 mg/dL |
| Phosphate       | 4.6 | 4.5-6.5 mg/dL  |
| Uric acid       | 3.4 | 4.5-8.2 mg/dL  |
| Albumin         | 3.1 | 3.5-5.0 g/dL   |
| Total Protein   | 6.0 | 6.4-8.3 g/dL   |

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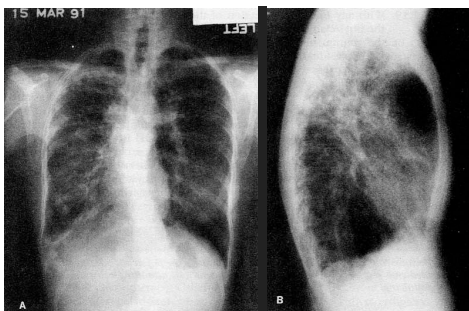
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### MB Chest Radiograph



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**MB**

- Read the chest radiograph.
- How do you interpret the ABGs?
- Why are the WBC and the number of band neutrophils elevated?
- What do a low albumin and total protein level indicate?

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**MB**

- Name additional diagnostic tests that would be important to perform on this patient.
- If the physician decides to admit this patient to the hospital, what respiratory therapy orders would you suggest?

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**MB**

- Because MB failed to improve on oral antibiotics her physician admitted her to the medical service for more aggressive treatment. The admitting orders included the following:
  - Supplemental vitamins A, D, and K
  - Aminophylline 1 g in 0.25 L NS con't IV
  - Piperacillin IV 1 g q6°
  - Amikacin 225 mg IVq8°
  - HHN Rx w/0.5 mL albuterol in 3 mL NS q6°

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**MB**

- CPPD q6°
  - Theophylline level on day 2
  - Amikacin level before and after the 3<sup>rd</sup> dose
  - Sputum for Gram stain and culture
  - Sweat chloride concentration
  - Gene probe for the delta F<sub>508</sub> gene
- The physician believes that MB may have CF. Why did he prescribe the supplemental vitamins?

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**MB**

- What is albuterol? What side effects may the patient experience while you administer this treatment?
- Is the CPPD important for this patient, or should you recommend that it be discontinued? Why?
- What is the most important thing that you as an RCP could teach this patient/parents to help long-term?

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**MB**

- If this patient has CF, what organism would you expect to find on sputum culture?
- One of the microorganisms that patients with CF commonly have as a respiratory pathogen has a unique characteristic. Describe what is unique about *Pseudomonas aeruginosa* found in CF?
- If MB has CF, what are the odds that she will have both copies of the delta F<sub>508</sub> gene?

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## MB

- MB is hospitalized for 5 days. During this time she receives antibiotics, bronchodilators, and CPT. Her symptoms were greatly improved with a marked reduction in her cough and dyspnea. She now produces far less sputum, and the color is a light yellow. Her parents have been trained to administer her bronchodilators, IV antibiotics and to perform CPT. The sputum culture grew a mucinous strain of *P. aeruginosa* that was resistant to ciprofloxacin. Her sweat chloride concentration was 103 mEq/L. The gene probe revealed that MB had only 1 copy of the delta F<sub>508</sub> gene.

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## MB

- Does MB have CF?
- MB is not unusual for patients with CF. Her presentation contained many classic features of the disease but also lacked a significant number of common abnormalities. Pancreatic insufficiency is 1 typical finding she does not have. Patients with normal pancreatic exocrine function have a better prognosis than those with pancreatic dysfunction.

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## Pathophysiology

- In GI tract
  - Abnormalities in the pancreatic duct & glands lead to inadequate absorption & digestion of food
    - ↓
    - Diabetes
    - Malnutrition - "failure to thrive"
    - Foul-smelling stools

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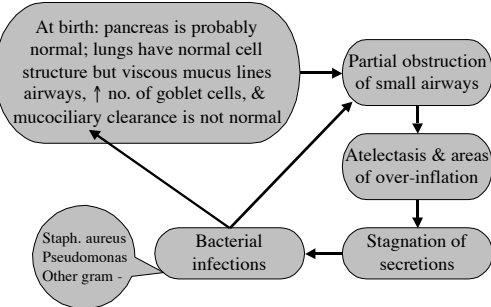
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## Pathophysiology



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## Eventually --

Bronchitis  
Bronchiolitis  
Bronchiectasis → accompanied by bronchial artery hypertrophy  
Bronchiolectasis ↓  
Overinflation mild-to-fatal hemorrhage  
Atelectasis  
Bleb formation (upper lobes) → pneumothorax  
Fibrosis  
Cor pulmonale  
↓  
Cardio-respiratory insufficiency  
↓  
Death

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## Diagnosis

- Median age of Dx = 6 mo.
- Based on positive lab testing + clinical conditions consistent with CF or family history
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## Diagnosis

- Lab Testing
  - Increased sweat chloride ( $> \text{ mEq/L}$ ) on 2 separate occasions
  - DNA testing (CFTR gene analysis)
  - Nasal Electrical Potential Difference - new; measures difference in voltage potentials across the nasal epithelium
  - Newborn screening - not done routinely; measurement of serum immunoreactive trypsinogen from a heel stick (elevated in pancreatic insufficiency)

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## Treatment

- Requires a very comprehensive approach & early, aggressive Rx
  - GI, dietary, psychosocial
- Pulmonary treatment aimed at reducing infections & removing thick, viscous secretions

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## Treatment

- Oxygen
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## Treatment

- Antibiotic therapy to treat infections
  - Acute and long-term
    - aminoglycoside (Gentamicin)
      - +
    - fluorinated quinolones
      - ciprofloxacin (Cipro)
      - levofloxacin (Levoquin)
      - moxifloxacin (Avelox)
      - gatifloxacin (Tequin)
  - aerosolized tobramycin & gentamicin effective against *Pseudomonas*

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## Treatment

- Aerosol drug therapy
  - Bronchodilators (may help)
    - Do PFT before & after to determine response
    - Studies have shown good response to
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      - \*\*                      \*\*
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## Treatment

- Aerosol drug therapy
  - Mucolytics
    - Alter adhesiveness of mucus
      - Pulmozyme (dornase alfa)
      - Recombinant DNase (rhDNase)
      - Mucomyst - not effective because causes bronchospasm
  - Amiloride
    - Sodium channel blocking diuretic
    - Aerosolized to CF patients
    - Increases secretion clearance by inhibiting abnormal sodium absorption
    - Doesn't alter course of CF

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## Treatment

- Aerosol drug therapy
  - Wetting agents
    - Nebulized hypertonic saline
      - Can cause bronchospasm so must premedicate with bronchodilator
    - Sodium bicarb
  - May be helpful but are not first line defense

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## Treatment

- Anti-inflammatory therapy
  - Cromolyn sodium (Intal) and inhaled corticosteroids, esp. budesonide (Pulmicort) may help
  - High-dose ibuprofen (seems to slow the progression of the disease)

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## Treatment

- CPT
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- PEP therapy
- FET
- Autogenic drainage
- Exercise

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## Treatment

- Diet
  - Lipase, protease & amylase to aid in digestion of fats, proteins & carbs
  - 2 x normal amount of protein & calories to maintain proper growth
  - Vitamins
- Heart-lung transplant
  - If cor pulmonale + severe CF
  - No evidence of disease redevelopment, however do have the problems associated with rejection, immunosuppression

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## Treatment

- CMV
  - Presents special problems
  - With ↑ airway obstruction & frequent bacterial infections, long-term prognosis is reduced once a CF patient is placed on CMV
  - Problems reduced with NIPPV (BiPAP , nasal CPAP)

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## Treatment

- Gene therapy
  - Researchers are focusing on ways to correct the defective gene, or correcting the defective protein
  - Correct faulty CFTR genes by adding normal copies of the gene to laboratory cell cultures
  - modified a common cold virus to act as a delivery vehicle - or "vector"- carrying the normal genes to the CFTR cells in the airways of the lung
  - subsequent studies have tested other methods of gene delivery, such as fat capsules, synthetic vectors, nose drops or drizzling cells down a flexible tube to CFTR cells lining the airways of lungs - researchers are now testing aerosol delivery using nebulizers

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## Treatment

- Sounds easy!?
  - finding the best delivery system for transporting normal CFTR genes is only one problem that scientists must solve to develop an effective treatment for CF - scientists must also determine the life span of affected lung cells, identify the "parent cells" that produce CFTR cells, find out how long treatment should last and how often it needs to be repeated

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## Outlook

- Great advances made in last 15 years including gene therapy
- Life expectancy has risen from 4-6 years to young adulthood
  - Median survival age today is

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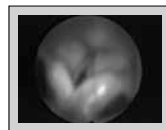
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## Final Exam



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