Cystic Fibrosis

**CYSTIC FIBROSIS:**
- Autosomal recessive disorder
- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)
  - ATP binds to it → conformational change → chloride channel opens up → sodium and water follows chloride
  - In CF, chloride is unable to be transported across membrane → sodium and water can’t follow → affects mucus hydration

**DIAGNOSIS:**
- Sweat test: Gibson Cooke procedure
  - **Sweat Chloride** | **Diagnosis**
    - < 30 mmol/L | Negative
    - 30 – 60 mmol/L | Borderline < 6 mo
    - 40 – 60 mmol/L | Borderline > 6 mo
    - > 60 mmol/L | Positive
- Newborn Screening (NBS): *immunoreactive trypsinogen* (IRT)
  - Enzyme released by pancreas
  - If elevated, is an increased risk for CF
- Fecal Elastase: test for pancreatic function
  - Pancreatic insufficiency (PI) = deficient fecal elastase (measured in stool)
    - **Fecal Elastase** | **Pancreatic Function**
      - > 200 ug/g | Normal
      - 100 – 200 ug/g | Mild – mod exocrine PI
      - < 100 ug/g | Severe exocrine PI

**PHARMACOKINETICS IN CF:**
- **A**
  - ↓ NaHCO_3_ secretion, ↓ gastric pH
  - Delayed gastric emptying
- **D**
  - ↑ Vd
- **M**
  - ↑ hepatic blood flow
  - Induction of hepatic enzymes
- **E**
  - ↑ GFR
  - ↑ tubular secretion
  - ↓ tubular reabsorption

**BOTTOM LINE:** CF patients need higher doses and increased dosing frequency

**CFTR MUTATION CLASSES:**

<table>
<thead>
<tr>
<th>Class</th>
<th>CFTR</th>
<th>CFTR Protein</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Protein synthesis defect (premature stop codon)</td>
<td>Little to no CFTR on cell surface → no or little chloride transport</td>
<td>Mucus layer is quite thick</td>
</tr>
<tr>
<td>II</td>
<td>Protein folding or trafficking defect</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Gating defect that impairs opening of the channel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Structural defect that decreases Cl(^-) conductance (ex/ narrowing of channel)</td>
<td>Some chloride transport; in some mutation pairs, it can almost be at normal function</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Splicing defect that results in a reduced number of functional CFTR at cell surface</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Decreased stability of CFTR resulting in increased cell surface turnover and CFTR degradation</td>
<td>Depends on what mutation it is combined with</td>
<td></td>
</tr>
</tbody>
</table>

**CYSTIC FIBROSIS PRESENTATION:**

| Sinuses | • Sinusitis  
| Nasal polyps |
| Lungs | • Airway obstruction  
| Bronchiectasis  
| Pneumothorax  
| Hemoptysis |
| Liver | • Obstructive biliary tract disease |
| Pancreas | • Enzyme insufficiency  
| Insulin dependent diabetes |
| Small intestine | • Meconium ileus  
| Distal intestinal obstruction syndrome  
| Rectal prolapse |
| Reproductive tract | • Male infertility (congenital absence of vas deferens) |
| Skin | • Sweat Cl\(^-\) > 60 mmol/L |
Cystic Fibrosis

**PANCREATIC INSUFFICIENCY:**

**PATHOGENESIS:**
1. Thick mucous blocks pancreatic duct
2. Impaired pancreatic enzymes & bicarbonate secretion into duodenum
3. Progressive pancreatic damage and atrophy

**S/S:**
- Fat malabsorption
- Oily, large, foul smelling stools
- Malnutrition
- Poor weight gain
- Fat soluble vitamin deficiency

**GOALS OF THERAPY:**
- Increase and optimize absorption of fats, nutrients & fat soluble vitamins
- Normalize bowel movements
  - Normalize frequency
  - Decrease steatorrhea
- Optimize growth & weight gain

**SALT SUPPLEMENTATION:** REQUIRED for replacing salt losses (sweat) & for growth
- Home-made recipe salt solution provided for babies
- Older children & adults supplement by salting foods
- Sodium chloride capsules (1g/cap) for hot weather / activity

**DOSE:** 2-4 mmol/kg/day
> Monitor urinary Na: > 30 mmol/L

**FAT SOLUBLE VITAMINS:** Vitamins A, D, E, K
- Newborns start combination ADEK products AFTER ALBUMIN IS NORMALIZED
  > Albumin is a marker for retinol bind protein, which binds vitamin A
  > Without RBP, high vitamin A → pseudotumor cerebri
- NOTE: MVW Complete Formulation from USA is approved through Health Canada Special Access Program
  > No ADEK product in Canada because K > 1 mg = Rx
  > Covered by PharmaCare Plan D
- Nutritional parameters monitored annually (unless otherwise indicated)

**IMMUNIZATIONS:**
- All routine immunizations
  - Additional pneumococcal conjugate vaccine at 6 months (Prevnar-13)
  - Pneumococcal polysaccharide vaccine > 2 years (Pneumovax-23)
- Annual influenza vaccine (> 6 months)
- Respiratory Synctial Virus (RSV) prophylaxis – Palivizumab (Synagis)

**PANCREATIC ENZYMES:** replacement therapy to supplement pancreatic enzymes (lipase, amylase, protease)
- **Coated enzymes:** bypass acidic stomach → enters duodenum where enzymes are released in the basic pH
- **Non-coated enzymes:** used only for patients on tube feeds
  - Crushed & suspended in water → added to feeds to predigest the feed prior to administration

**DOsing:**
- 500-2500 units of lipase/kg/meal
  - Half the standard dose for snacks
  - MAX: 10000 units lipase/kg/meal (from all meals & snacks)
- Enzymes active for 2 hours after ingestion
- Dosing varies based on pt reported symptoms (stool), growth parameters

**ADVERSE EFFECTS:**

<table>
<thead>
<tr>
<th>Dose too high</th>
<th>Dose too low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation, impaction</td>
<td>Steatorrhea, diarrhea</td>
</tr>
<tr>
<td>Mucosal irritation</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Fibrosing colonopathy → colonic strictures (high dose, long term)</td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia and hyperuricosuria</td>
<td></td>
</tr>
<tr>
<td>Perianal irritation (especially if in diapers)</td>
<td></td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td></td>
</tr>
<tr>
<td>Allergy/hypersensitivity to porcine (pork) protein</td>
<td></td>
</tr>
</tbody>
</table>

> Do not store in heat → enzyme activity higher
> Do not take with milk products (alkaline = released earlier)

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### Respiratory: Pulmonary Exacerbations

#### Vicious Cycle of Infection and Inflammation:

- Defective CF gene
- Defective/difficient CFTR (chloride transport not going into airway mucus, so its thick mucus
- Abnormal airway surface environment (cells can’t bring out mucus or other bacteria
- Bronchial obstruction
- Infection
- Inflammation
- Information to fight the infections
- Destruction of the lung

#### S/S: of pulmonary exacerbation

- **Pulmonary**
  - Dyspnea
  - ↑ work of breathing
  - ↑ RR
  - Wheezing
  - Chest congestion
  - ↑ cough
  - Sputum
  - Hemoptysis
  - ↓ lung function by 10%
  - ↓ exercise tolerance

- **Upper respiratory**
  - Sore throat/runny nose
  - Sinus pain/ tenderness
  - Sinus discharge color

- **Other**
  - Malaise/fatigue/lethargy
  - Abdominal pain
  - Fever
  - ↓ appetite
  - ↓ weight
  - School absenteeism

#### Pulmonary FXN Tests:

- ↓ FVC = obstruction or restriction
- ↓ FEV₁ = obstruction
- ↓ FEF₂₅₋₇₁ = obstruction
  - Mean forced expiratory flow during middle half of FVC
  - Indicative of small-medium airways

#### GOALS OF THERAPY:

- To optimize pulmonary function
- To decrease number of pulmonary exacerbations
  - To decrease / thin mucus secretions
- To return pulmonary function to pre-exacerbation status
- To prolong time to lung bacteria colonization
- To prevent progression of inflammatory changes in the lung

#### THERAPY:

<table>
<thead>
<tr>
<th>Tax</th>
<th>Examples</th>
<th>Effectiveness</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilators</td>
<td>β₂ agonists (salbutamol, formeterol)</td>
<td>To prevent bronchospasm &gt; Especially when other inhaled meds can cause bronchospasm (7% hypertonic saline)</td>
<td>Relax and open airways, allowing inhaled meds in</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Corticosteroid</td>
<td>Only when indicated (asthmatic like component) or if pt improvement in lung function</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>≥ 6 yo with Pseudomonas persistently present in culture of airways (50% of cultures positive in previous year)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>In US &gt; 6 yo with FEV₁ &gt; 60% predicted to slow loss of lung function&lt;br&gt;Not routinely done in Canada based on age (select pts may be trialed)</td>
<td></td>
<td>GI pain or bleed&lt;br&gt;Renal failure</td>
</tr>
<tr>
<td>Mucolytics</td>
<td>Pulmozyme</td>
<td>Recombinant human deoxyribonuclease I → selectively hydrolyzes and cleaves DNA to decrease sputum viscosity&lt;br&gt;Dose: 2.5 mg/2.5 mL nebulized daily or BID</td>
<td></td>
</tr>
<tr>
<td>7% sodium chloride for inhalation (hypertonic saline)</td>
<td>Concentrates sputum, drawing free water into sputum to decrease sputum viscosity&lt;br&gt;Dose: 4 mL nebulized BID</td>
<td></td>
<td>Bronchospasm (minimize risk by mixing salbutamol 5 mg/mL and nebulize together OR administer salbutamol MDI with spacer prior to nebulizing)&lt;br&gt;Cough&lt;br&gt;Salty taste</td>
</tr>
</tbody>
</table>

**ORDER:** salbutamol + 7% hypertonic saline → chest physio → ICS + inhaled abx + pulmozyme
### RESPIRATORY INFECTIONS:

**S. aureus**
- Gram positive cocci
- First bacterial pathogen to colonize respiratory tract
- Development of inflammation, tissue destruction and lung injury
  - Predisposes to infection by other pathogens (Pseudomonas)
- **ERADICATION OF S. AUREUS**
  - Prophylaxis unsuccessful in past, so treat only if cough swab culture positive for S. aureus

### ANTIBIOTIC CHOICES:

<table>
<thead>
<tr>
<th>ANTIBIOTIC</th>
<th>NOTES</th>
</tr>
</thead>
</table>
| Cloxacillin | • Empty stomach, QID dosing  
  • Unpalatable (reserved for older pts as liquid is unpleasant) |
| Cephalexin | • Unaffected by food, QID dosing |
| SMX/TMP | • Unaffected by food, BID dosing  
  • Dosed using TMP component  
  • AVOID in first 2 months of life  
  • SMX displaces bilirubin from albumin → bilirubin crosses BBB → kernicterus |

### PSEUDOMONAS AERUGINOSA (PA):
- Gram negative bacteria; ubiquitous, found in water reservoirs
- Opportunistic pathogen in CF: enters lungs via oral/nasal passages → travels to airway, binds to mucus layer → unable to clear with non-functioning cilia → inflammatory response triggered
- Initial infection with non-mucoid PA
  - **Mucoid PA**: colonization with PA → formation of alginate polysaccharide layer around micro-colonies → anaerobic environment
    - Defense mechanism of PA: abx unable to penetrate & resistant to phagocytosis
    - Azithromycin given M/W/F (PA is not susceptible but prevents formation of mucoid layer)
- Predictor of morbidity & mortality
  - Increased mortality, lower lung function, lower weight percentile, higher rates of PA isolation, more hospitalizations for acute pulmonary exacerbations
- **ERADICATION OF PA**

### ANTIBIOTIC CHOICES:

<table>
<thead>
<tr>
<th>PENCILLINS</th>
<th>CARBAPENEMS</th>
<th>MONOBACTAMS</th>
<th>AMINOGLYCOSIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloxacillin, ticarcillin-clavulinate</td>
<td>Imipenem-cilastatin, Meropenem</td>
<td>Aztreonam</td>
<td>Tobramycin, Gentamicin, Amikacin</td>
</tr>
</tbody>
</table>

### ERADICATION PROTOCOLS:

- **Outpatient if “well”**
  - Tobramycin inh soln x 28 days PLUS Cipro (PO) x 3 wks
- **Inpatient if “unwell”**
  - 2 weeks IV abx → step down to outpatient therapy
- **IF ERADICATION FAILED**
  - 2nd attempt either outpatient or hospital (as above)
- **IF 50% cultures in last 12 months still positive...**
  - PATIENT IS COLONIZED WITH PA

### INHALED ANTIBIOTICS FOR COLONIZED PA:

<table>
<thead>
<tr>
<th>PENICILLINS</th>
<th>CARBAPENEMS</th>
<th>MONOBACTAMS</th>
<th>AMINOGLYCOSIDES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>Colistin</td>
<td>Aztreonam</td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

### HOW LONG TO TREAT INFECTIONS IN CF:
- **required 10-14 days** to achieve peak FEV1; longer txt may be required to recover FEV1 (especially if baseline FEV1 is low)
**RESPIRATORY: OTHER**

**HEMOPTYSIS:**

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scant ≤ 5 mL</td>
<td>Hospitalization or management as outpt</td>
</tr>
<tr>
<td>Mild-mod 5 – 240 mL</td>
<td>Antibiotics</td>
</tr>
<tr>
<td>Massive &gt; 240 mL</td>
<td>Stop agents that affect platelet function (NSAID)</td>
</tr>
<tr>
<td></td>
<td>Modify airway clearance techniques</td>
</tr>
<tr>
<td></td>
<td>Vitamin K if INR is elevated</td>
</tr>
<tr>
<td></td>
<td>Transexameric acid (IV or PO) Displaces plasminogen from fibrin → inhibits fibrinolysis → stabilize clots formed to prevent further bleeds</td>
</tr>
<tr>
<td></td>
<td>Bronchial Artery Embolization (surgical) Bleeding artery identified via CT scan with contrast → insert catheter into artery → inject tiny beads</td>
</tr>
</tbody>
</table>

**LUNG TRANSPLANT:**

- FEV₁ < 30% = candidate for lung transplant
  - MUST be adherent to meds
- Survival for having transplant in 3 years is 22%, reaches 50% in 10 years
  - Survival for NOT having transplant in 3 years is 50%

**GASTROINTESTINAL:** Gastroesophageal Reflux Disease (GERD) & Gastric motility (delayed gastric emptying)

**PATHOPHYSIOLOGY:**

**GERD**

- Lower esophageal sphincter:
  - ↓ pressure
  - ↑ relaxation
  - Risk for aspiration into lungs

**Delayed Gastric Emptying**

- Multifactorial
  - Small intestinal bacterial overgrowth
  - Luminal viscosity
  - Inflammation
  - Gastric secretions thicker → harder to move
  - At risk for malabsorption and constipation

**S/S:**

- Poor weight gain
- Large and frequent spit-ups
- Heartburn, regurgitation
- Voice hoarseness
- Chest pain
- Coughing
- Wheezing

**GOALS OF THERAPY:**

- To minimize sx of GERD
- To maximize absorption of nutrients
- To maximize growth
- To prevent aspiration

**TREATMENT:**

- H₂-Receptor blockers: ranitidine
- PPIs: omeprazole for peds; requires special authority
- Gastric motility agents: domperidone or metoclopramide; bethanechol; cisapride (CYP3A4 drug interactions)
  - QTc prolongation = ECGs required (pre-treatment, post-treatment x 1 wk, then 6 mo, then yearly)

**GASTROINTESTINAL:** DISTAL INTESTINAL OBSTRUCTION SYNDROME (DIOS) – due to thickened stools

- Sx: constipation, abdominal pain, decreased intake, vomiting (bilious)

**RISK FACTORS:**

- Dehydration (summer)
- Rapid increase in enzyme dosage
- Poor adherence with enzyme therapy
- Pancreatic insufficiency & severe genotype
- Previous history of DIOS
- CF related diabetes
- Post-transplant

**TREATMENT:**

- Hospital: rehydration, enemas (N-acetylcysteine, polyethylene glycol with electrolytes, sodium phosphate), pain management
- Chronic DIOS: polyethylene glycol, lactulose, N-acetylcysteine
  - N-acetylcysteine: mucolytic agent (sulfuric acid group interacts with disulfide bonds in mucoproteins)
    - IV given orally mixed with water, orange juice, coke...
    - Compounded form: “strawberry cream sail”
    - Capsule form sold as NHP

**MECONIUM ILEUS**

- Complication in a newborn (that is even worse in CF patients)
- Meconium – newborn stool (black and sticky already)
  - Impaired Cl⁻ transport in CF patients results in even more thick & sticky meconium
  - May cause intestinal blockage
- S/S: abdominal distension, bilious vomiting, no passage of meconium
- Management: enemas (rectal & oral to target from both sides of blockage); rehydration; surgical
## GASTROINTESTINAL: CF-RELATED LIVER DISEASE
- 5-10% CF patients develop multi-lobar cirrhosis during first decade

### PATHOGENESIS:
1. Sludge in biliary tract
2. Biliary obstruction
3. Focal cirrhosis
4. Multi-lobar cirrhosis

### GOALS OF THERAPY:
- To delay liver disease progression (portal hypertension, variceal bleed, cirrhosis)
- To encourage regression of hepatic lesions (steatosis)

### TREATMENT:
- Ursodeoxycholic acid up to 30 mg/kg/day
  - Soluble, hydrophilic bile acid → promotes biliary drainage
  - Decreases cholesterol synthesis, secretion, absorption
- Risk for bleeding: thrombocytopenia
  - Vitamin K supplementation

## GASTROINTESTINAL: CF RELATED DIABETES
- Screening yearly starting at age 10
- In-between type 1 & 2 diabetes:
  - Still have insulin production – not all beta cells destroyed yet
  - Some degree of insulin resistance – increased when having a pulmonary exacerbation

### PATHOGENESIS:
1. CFTR deficiency/abnormality → increased viscosity of pancreatic excretions
2. Obstructive damage to pancreas
3. Progressive fibrosis & fatty infiltration
4. Islet cell destruction, progressive decline of beta-cell mass
5. Primary insulin deficiency

### S/S:
- Hyperglycemia
  - ↑ urinary frequency
  - Polydipsia
  - Polyphagia
  - Fatigue
  - Weight loss
  - ↑ pulmonary exacerbations
  - ↓ lung function

### TREATMENT:
- Long-acting insulin
- Short acting insulin (once they lose insulin production)
- Sliding scale
- Frequent monitoring, especially when unwell

## OTHER MANIFESTATIONS:
### NASAL POLYPS:
- Small growths within nostril due to chronic inflammation of nasal mucosa
- S/S: nasal congestion, nasal blockage, facial pain, loss of sense of smell, decreased appetite
- Txt: surgical (polypectomy), intranasal corticosteroids (mometasone, fluticasone), saline nasal rinses (+/- antibiotics)

## NUTRITIONAL DEFICIENCIES:
- Iron (→ anemia), magnesium & zinc deficiency
- Maximize calories
  - Nutritional supplements/drinks
  - Tube feeds (formula)

## MUSCOSKELETAL:
- Arthritis: managed by rheumatology
- Osteoporosis: screening at 10 years old
  - DEXA scan
  - Adequate calcium & vit D intake
  - Non-drug: weight bearing exercise, maintain good BMI, limit caffeine (↑ calcium exertion)
  - Bisphosphonates (alendronate, pamidronate)

### CONGENITAL BILATERAL ABSENCE OF VAS DEFERENS:
- Mucus that is produced in the vas deferens is thick and sticky → clogs vas deferens as they are forming, causing them to deteriorate before birth
- Testes still produce sperm, but unable to be transported and become part of semen
- INFERTILITY
## CFTR MODULATORS – new CF treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MOA</th>
<th>Efficacy</th>
<th>Dosing</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor</td>
<td>CFTR potentiator</td>
<td><em>Promising drug</em></td>
<td>≥ 6 yo: 150 mg tab BID</td>
<td>Major CYP3A4 substrate</td>
</tr>
<tr>
<td></td>
<td>• Works on gating mutations</td>
<td>• Lung damage is reversible, so even though this fixes underlying defect of CFTR, they still need to continue with regular CF treatments</td>
<td>2-6 yo: 50 mg and 75 mg granule sachets</td>
<td>Inhibitor of CYP enzymes, p-gp</td>
</tr>
<tr>
<td></td>
<td>• Induces CFTR channel opening, and allows passage of Cl⁻</td>
<td></td>
<td>Taken with a fatty meal to increase absorption</td>
<td></td>
</tr>
<tr>
<td>Lumacaftor – Ivacaftor</td>
<td>CFTR corrector + CFTR potentiator</td>
<td>• Lumacaftor on its own did not work because channel would not open</td>
<td>≥ 12 yo: 200/125 mg tab (2 tab BID)</td>
<td>Lumacaftor: CYP3A4 inducer</td>
</tr>
<tr>
<td></td>
<td>• For F508del homozygous mutation</td>
<td>• Not much better than Ivacaftor alone</td>
<td>Taken with a fatty meal to increase absorption</td>
<td>Ivacaftor: CYP3A4 substrate and inhibitor</td>
</tr>
<tr>
<td></td>
<td>• Lumacaftor increases processing and folding of F508del → increasing amount of CFTR at cell membrane</td>
<td></td>
<td></td>
<td>NET: CYP3A4 inducer</td>
</tr>
<tr>
<td></td>
<td>• Ivacaftor opens channel and allows passage of Cl⁻</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataluren</td>
<td>• For nonsense mutation (premature stop codon)</td>
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<tr>
<td></td>
<td>• Helps to read through premature stop codon, and produces full length CFTR protein</td>
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</tr>
</tbody>
</table>

## ADHERENCE

**POOR ADHERENCE:** nebulized therapy can take up to 2 hours BID (= 4 h/day) & oral therapy is up to 50 pills/day
- ↑ morbidity & mortality
  - ↑ pulmonary exacerbations
  - ↓ baseline lung function
- ↑ utilization of healthcare
  - ↑ hospitalizations
  - Longer hospital stay
- ↓ quality of life

**ADHERENCE:**
- Pharmanet record
- Electronic charting
- Tools
  - Apps
  - Alarms
  - Medication Administration Record
  - Medication Calendar (blister packing)
  - ROUTINE