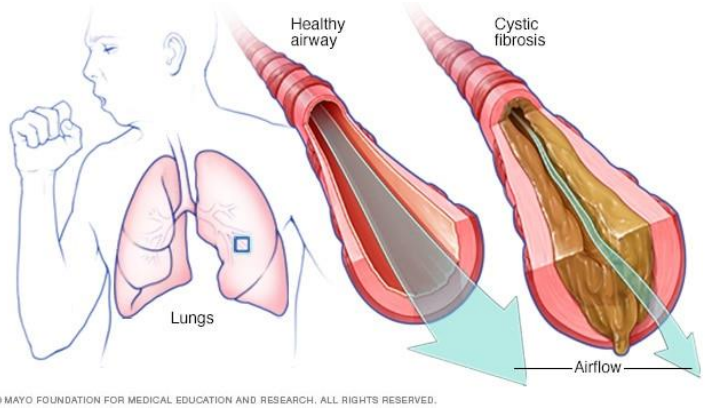


Image taken from: https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700#dialogId61259186

Cystic Fibrosis (CF)

Part 1 – Epidemiology & Pathophysiology

PC3303 – Integrated Therapeutics 3

Cassie Lanskey

Learning Objectives

- **Understand the pathophysiology of CF**
- List the drug treatment options
  - Place in therapy
  - Mechanism of action
  - Common adverse effects
  - Monitoring and counselling
- Understand the principles of infection prevention & treatment
- Apply this knowledge to a case study
  - Identify common clinical problems
  - Create a pharmaceutical care plan

Introduction

- The most common life-limiting genetic disease in Caucasians
  - In Australia, 1 baby is born with CF every 4 days (approx. 1 in 2,500 babies)
- Autosomal recessive genetic disease
- Complex multisystem disease
  - Affecting lungs, GI tract, sinuses, sweat glands, bones and reproductive organs

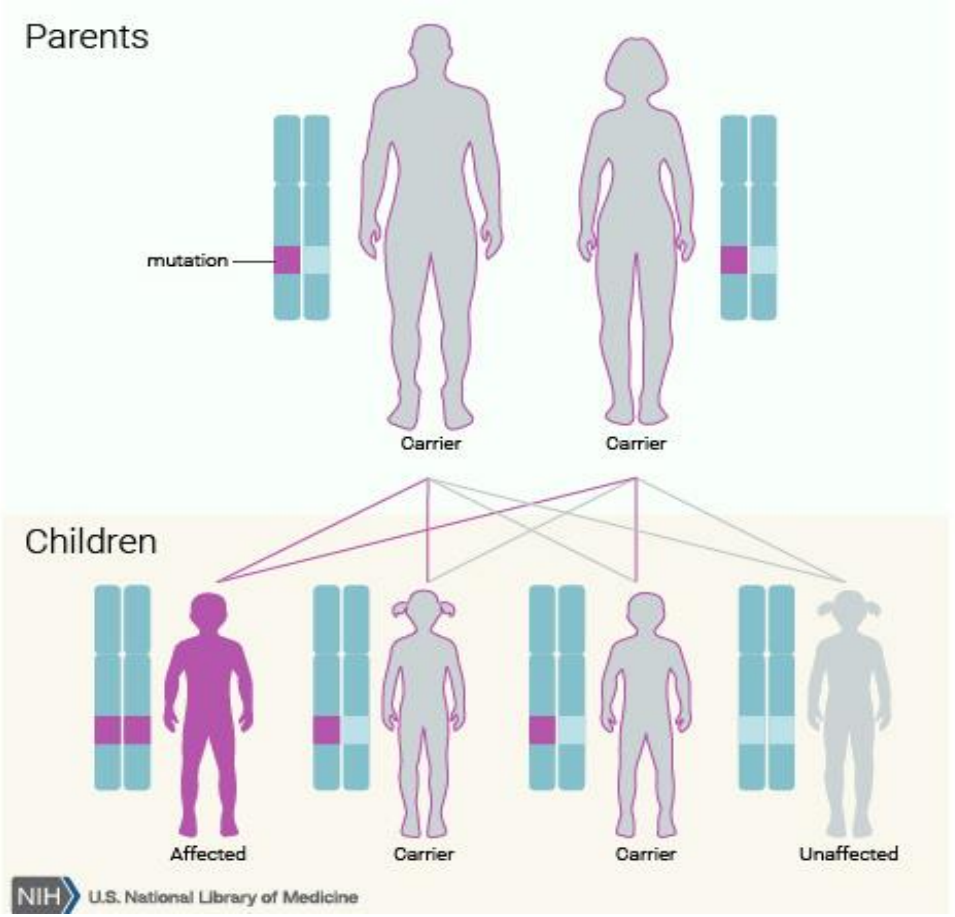


Image taken from: https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns

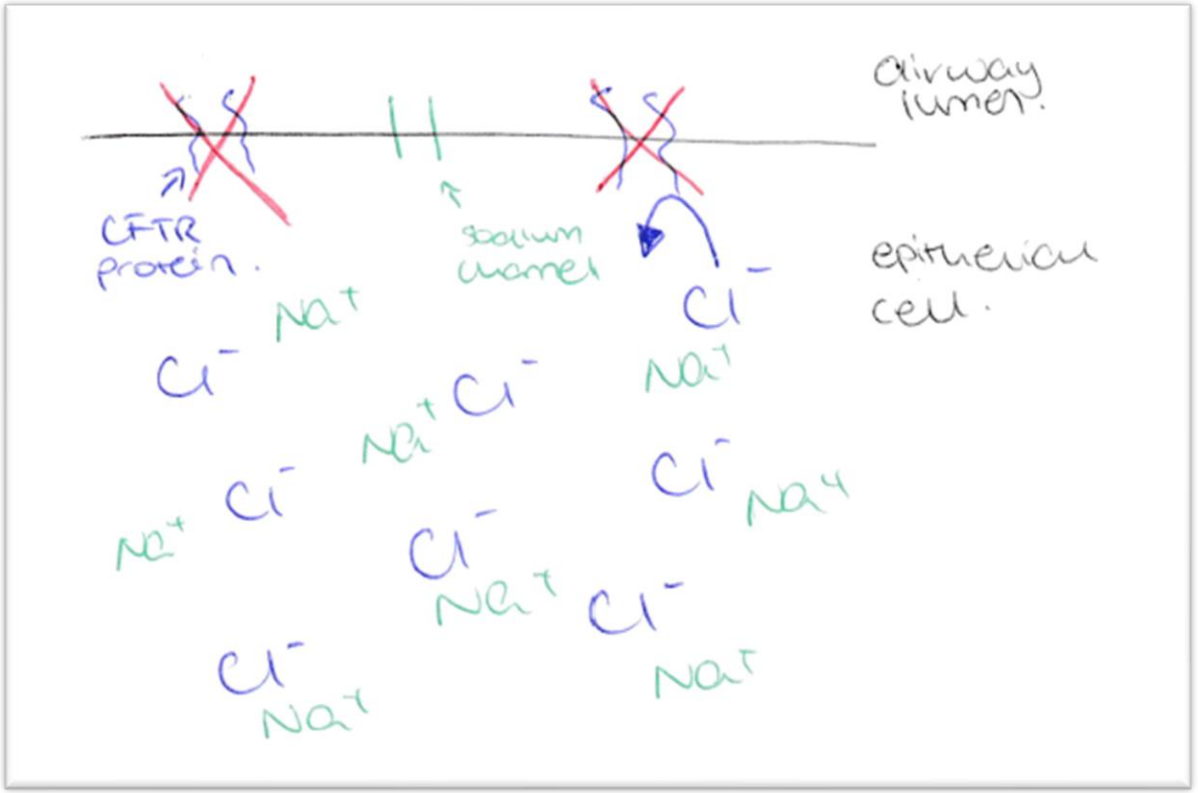
Pathophysiology

- The CF gene encodes a protein known as the cystic fibrosis transmembrane conductance regulator (CFTR)
- CF gene mutations → abnormal variants of CFTR protein
  - There are many different types of CF gene mutations possible → different types of CFTR variants each associated with different degrees of CF disease severity

https://www.youtube.com/watch?v=6IbP1ASGv9w&ab_channel=biointeractive

Pathophysiology of CF

- The CFTR protein <u>normally</u> functions to regulate the movement of chloride ions <u>out of cells</u> into the **airway or GI lumen**
  - Sodium ions follow the chloride ions.
  - Both attract a layer of water to promote fluidity & movement of secretions.
- <u>In CF</u>, the lumen surface is lacking Cl^-, therefore it is lacking Na^+ and H_2O (→)



Overview of Symptoms

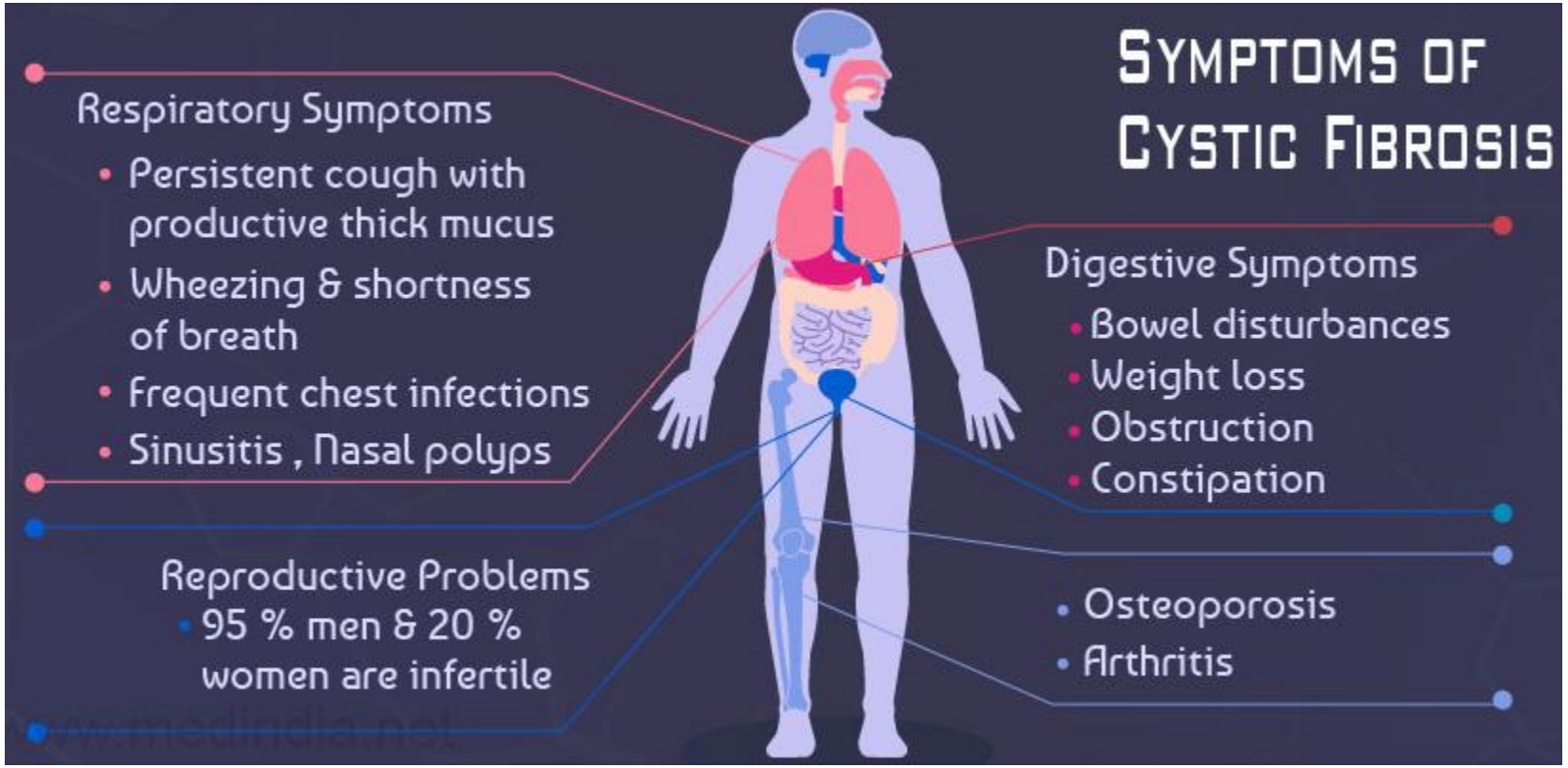


Image taken from: https://www.medindia.net/patients/patientinfo/cystic-fibrosis.htm

Diagnosis

- Newborn Screening Program
  - All children are tested at birth (via heel-prick blood sample)
- Infants with two CF mutations are referred directly to a specialist CF centre
- Infants with one CF mutation identified undergo a sweat test to determine if they have CF or if they are a simply a carrier of the gene mutation

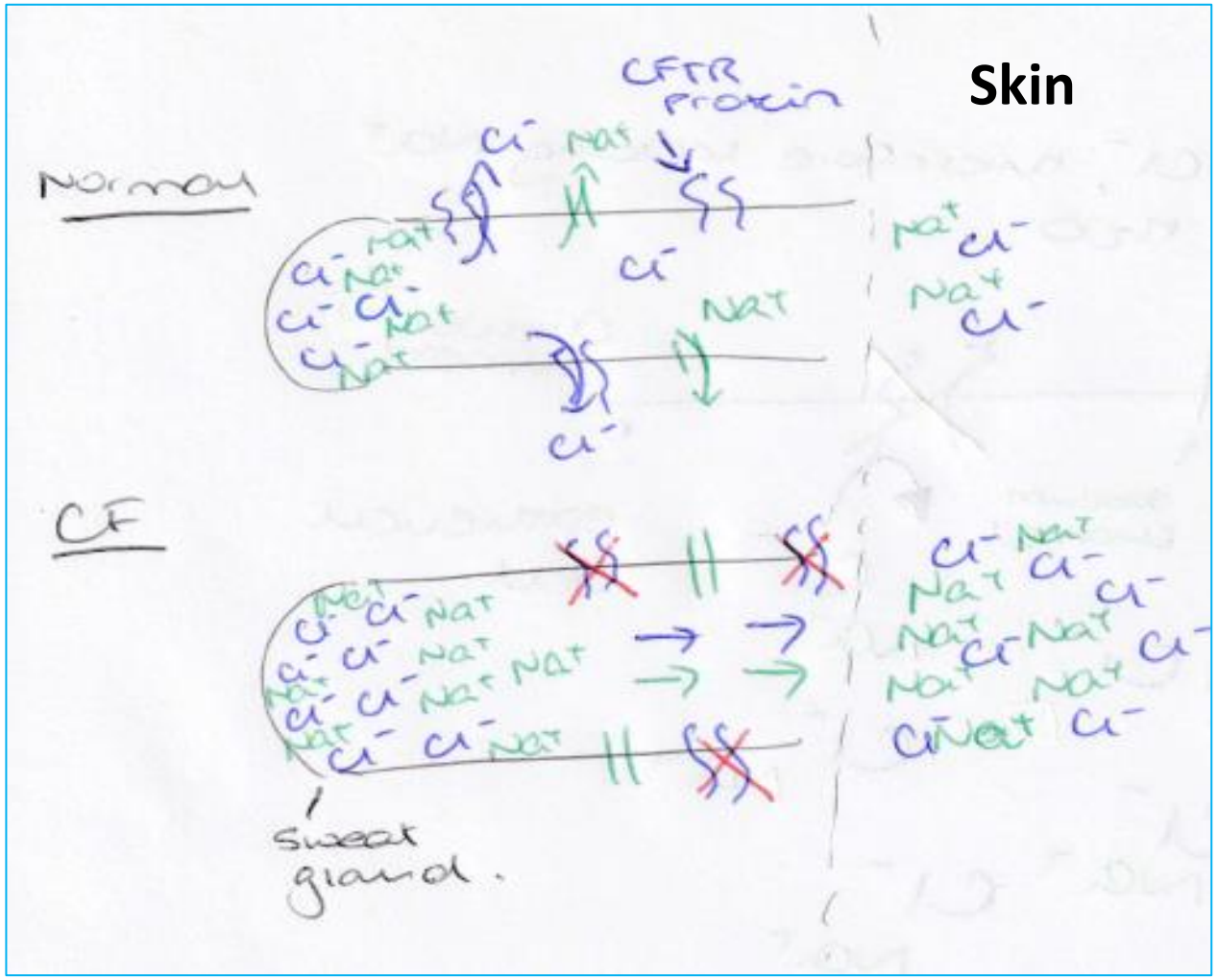


Image adapted from: https://www.youtube.com/watch?v=cu6rfyEMFiQ

Prognosis

- Depends on the type of CFTR mutation
- Previously, CF was considered primarily a paediatric disease
- Now, CF patients are surviving well into adulthood

- Medium survival time is ~35 years

- Better outcomes are attributable to better management strategies
- All CF patients are managed by (or in consultation with) a specialist CF centre
    - No changes to prescribed therapies are made without consulting this centre

Respiratory Goals

“Limit progression of lung damage caused by bacterial infection and neutrophilic inflammation”

Established treatment modalities include:

- Effective airway clearance
  - Chest physiotherapy and mucolytics
- Anti-inflammatory drugs
- Drugs to correct CFTR protein function
- Early aggressive antibiotic therapy
  - Heightened need to prevent development of antimicrobial resistance

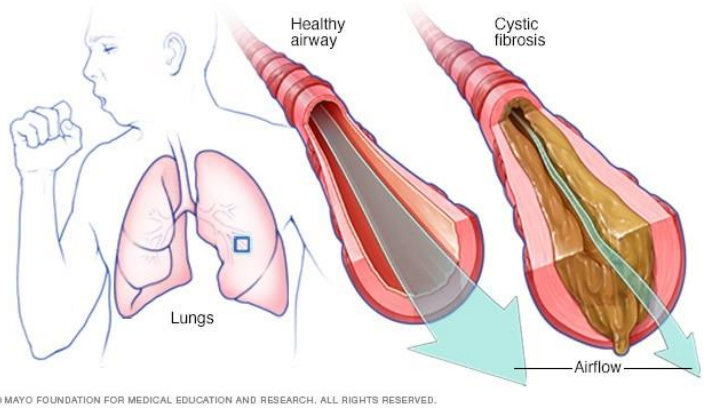


Image taken from: https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700#dialogId61259186

Cystic Fibrosis (CF)

Part 2 – Approach to Treatment

PC3303 – Integrated Therapeutics 3

Cassie Lanskey

Learning Objectives

- Understand the pathophysiology of CF
- **List the drug treatment options**
  - **Place in therapy**
  - **Mechanism of action**
  - **Common adverse effects**
  - **Monitoring and counselling**
- **Understand the principles of infection prevention & treatment**
- Apply this knowledge to a case study
  - Identify common clinical problems
  - Create a pharmaceutical care plan

Overview

1. Effective airway clearance
2. Anti-inflammatory drugs
3. Potentiator therapy with drugs to correct CFTR protein function
4. Infection control in CF
5. Optimising antibiotic therapy

1. Effective Airway Clearance

- Chest physiotherapy
- Exercise

- Beta-agonists
  - Short-acting beta-agonists may be used prior to chest physiotherapy and PRN if spirometry results improve post-SABA use
  - Long-acting beta-agonists may be used if there is evidence of associated asthma / LABA improves the patient’s symptoms

1. Effective Airway Clearance

- Nebulised mucolytics
  - Dornase alfa (Pulmozyme®)
    - Cleaves extracellular DNA released from dead neutrophils in the airways
    - Dose: 1 nebule (2.5mg) once daily
    - Adverse effects: voice alteration, pharyngitis, laryngitis, rash
    - Counselling: Do not dilute or mix with other drugs in the nebuliser
  - Hypertonic saline
    - Sodium chloride 6% solution
    - Adverse effects: may cause bronchospasm, pre-treatment with bronchodilators may be required
    - Counselling: Solution must remain sterile, discard unused portion of opened sachets
- Inhaled mannitol

2. Anti-inflammatory agents

- Azithromycin
  - Class: Macrolide
  - Used in patients with chronic *Pseudomonas aeruginosa* infection
  - Anti-inflammatory (augments neutrophil function) as well as antibiotic effect
  - Dose (Adult): Oral 250-500mg 3x/week
- Oral corticosteroids
  - Controversial
  - Serious adverse effects, e.g. growth suppression, diabetes, cataracts, osteoporosis
- Inhaled corticosteroids
  - Lacking evidence but may be used
  - Assess for benefit by monitoring for changes in spirometry results

3. Potentiator Therapy

- **Ivacafor** (Kalydeco®)
  - Increases channel opening of the CFTR protein, facilitating chloride ion transport across cell membranes
  - Only effective for patients with a certain type of CF gene mutation (i.e. approx. 8% of all patients with CF in Australia)
  - Dose (Adult): 150mg Oral BD
  - Adverse effects: Abdominal pain, diarrhoea, dizziness, headache, rash, upper respiratory tract infections, raised LFTs
  - Counselling: Monitor LFTs, take with a fatty meal

4. Infection Control in CF

- Respiratory pathogens are highly transmissible
- *Burkholderia cepacia* can be transmitted from an infected to a non-infected patient and it is especially difficult to treat

- Provide a single room for all CF patients where possible
- Hand hygiene
- Vaccination
- Avoid mould/ stagnant water

Image taken from: https://www.redbrick.me/review-five-feet-apart/

5. Antibiotic Therapy

- In children, infections are predominantly caused by *Staphylococcus aureus* and *Haemophilus influenzae.*
- In adolescents and adults, the predominant organism is *Pseudomonas aeruginosa.*
  - Initially, the *P. aeruginosa* is antibiotic-sensitive.
  - Once resistance develops, infection becomes chronic and antibiotic therapy may only suppress the infection (not eradicate it).

- Early, aggressive antibiotic therapy is essential to delay deterioration

5. Antibiotic Therapy

- *S. aureus and H. influenzae*
  - Oral antibiotics are often suitable
  - Duration is normally **2-4 weeks**
  - E.g. flucloxacillin, cefalexin, clindamycin, trimethoprim+sulfamethoxazole, or amoxicillin+clavulanate

- Initial *P. aeruginosa* infection
  - Goal is eradication until this is no longer possible and chronic infection takes hold
  - Duration is normally **2-3 months**
  - IV antibiotic treatment options may include piperacillin+tazobactam, ceftazidime, tobramycin
  - Adjunct treatment options may include oral ciprofloxacin or nebulised tobramycin

5. Antibiotic Therapy

- Chronic *P. aeruginosa* infection
  - Goal is to suppress infection and reduce morbidity
  - It is common to use inhaled tobramycin BD in a month-on/month-off regimen

Organism susceptibility to antibacterials: aminoglycosides, carbapenems, glycopeptides, lincosamides

Top of page

Organism susceptibility to antibacterials: aminoglycosides, carbapenems, glycopeptides, lincosamides

The following table provides a general guide to clinical antimicrobial susceptibilities. The table is intended to assist empirical selection of antimicrobials in the absence of laboratory confirmation of susceptibility; it is not a substitute for management advice from clinical microbiologists or infectious diseases specialists. Consider these data in conjunction with the clinical condition of the patient, site of infection, knowledge of local susceptibility patterns (which may vary) and evidence-based guidelines. Use the narrowest spectrum antibiotic that is effective to limit the development of antimicrobial resistance. When in doubt seek specialist advice.

The designation of susceptibility used in the table is 75% (an organism is deemed susceptible if at least 3 out of 4 cultures tested are susceptible to that antibiotic).

See also Anti-infectives

Download a PDF of this table

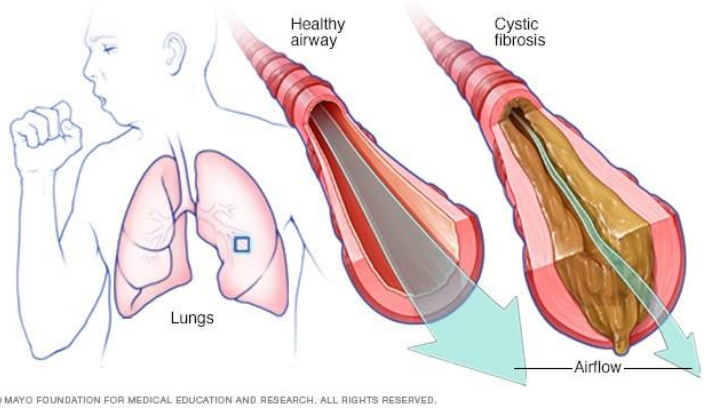
Click on the table below to enlarge

Organism	Aminoglycosides			Carbapenems			Glycopeptides		Lincosamides	
	amikacin	gentamicin	tobramycin	ertapenem	imipenem	meropenem	vancomycin	teicoplanin	clindamycin	lincomycin
Gram-negative										
Acinetobacter spp.										
Aeromonas spp.										
Burkholderia cepacia										
Burkholderia pseudomallei										
Campylobacter jejuni and *coli*										
Citrobacter freundii										
Enterobacter spp.										
Escherichia coli										
Haemophilus influenzae										
Klebsiella spp.										
Moraxella catarrhalis										
Morganella spp.										
Neisseria gonorrhoeae		1								
Neisseria meningitidis										
Pasteurella multocida										

Advanced Lung Disease in CF

- FEV1 < 30%

- Supplemental oxygen
- Non-invasive ventilation
- Lung transplant



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Cystic Fibrosis (CF)

Part 3 – Case Study

PC3303 – Integrated Therapeutics 3

Cassie Lanskey

Learning Objectives

- Understand the pathophysiology of CF
- List the drug treatment options
  - Place in therapy
  - Mechanism of action
  - Common adverse effects
  - Monitoring and counselling
- Understand the principles of infection prevention & treatment
- **Apply this knowledge to a case study**
  - **Identify common clinical problems**
  - **Create a pharmaceutical care plan**

Patient CF

- A 21-year old male
- Weight 54kg, eGFR > 90
- Presents to ED with shallow breathing, haemoptysis, increasing mucus, and increasing lethargy
- NKDA
- Past medical history
  - Cystic fibrosis
    - Severe lung disease
    - Chronic multidrug-resistant pseudomonas infection
  - Pancreatic insufficiency
  - Depression
- Non-adherent to prescribed medication regime

- Medications on admission

Medication name	Indication	Directions
Tobramycin (300mg/5ml) inhalation	Antibiotic	Nebulise and inhale 1 nebule twice a day for 1 month on and then one month off
Fluticasone/salmeterol 125/25microg inhaler	Improve control of airways disease	Inhale 2 puffs twice a day. Rinse mouth out with water after each use.
Sodium chloride 6% inhalation solution	Mucolytic	Nebulise and inhale 5ml of solution twice a day. Discard unused portion of sachets.
Dornase alfa (2.5mg/2.5ml) inhalation	Mucolytic	Nebulise and inhale 1 dose (2.5ml) at night
Salbutamol 100microg inhaler	Open airways	Inhale 2-4 puffs four times a day (before physiotherapy and when required)
Ivacaftor 150mg tablets	Improve lung function	Take 1 tablet twice a day with a fatty meal or snack
Pancreatic extract (Creon) 25,000 unit capsule	Pancreatic enzyme supplement	Take 1-10 capsules three times a day with meals *self-adjusted based on caloric intake as per directions from dietician*
Mirtazapine 30mg tablets	To assist mental health	Take 1 tablet at night

Medication Changes in Hospital

- **New**: IV Antibiotics (as per recommendations of Prince Charles Hospital CF Specialist)
  - Ceftazidime 3g Q8H
  - Tobramycin 320mg IV nocte

- **Withhold**: Dornase alfa (due to haemoptysis)

Patient CF

- A 21-year old male
- Weight: 54kg
- Presents to ED with shallow breathing, haemoptysis, increasing mucus, and increasing lethargy
- NKDA
- Past medical history
  - Cystic fibrosis
    - Severe lung disease
    - Chronic multidrug-resistant pseudomonas infection
  - Pancreatic insufficiency
  - Depression
- Non-adherent to prescribed medication regime

Infective Exacerbation of Resp. Symptoms

- ✓Airway clearance
  - SABA charted
- ✓Mucolytic
  - Hypertonic saline nebs charted, dornase alfa withheld
- ✓Anti-inflammatory
  - ICS charted as per pre-admission
- ✓Potentiator therapy
  - Patient qualifies for ivacaftor
- ✓Antibiotics as per specialist CF centre
  - Ceftazidime 3g Q8H
  - Tobramycin 320mg IV nocte

Pancreatic Insufficiency

- Pancreatic **exocrine** dysfunction
  - Dehydrated secretions → obstructed pancreatic ducts
  - Lack of pancreatic enzyme → inability to digest food/ absorb nutrients

  ✓Pancreatic enzyme supplements
    - Dose: Patients are trained to titrate the dose according to caloric intake and specialist/dietician
    - Capsules are to be swallowed whole or opened and sprinkled onto soft food and taken immediately (do not crush/chew)
    - Avoid hot food/liquid as this can destroy the enzymes

- Pancreatic **endocrine** dysfunction
  - CF-related diabetes
  - Do NOT restrict carbohydrates
  - Control BGL using insulin

Others

- Depression
  - Mirtazapine 30mg nocte
  - Offer social and professional psychological support
- Non-adherence
  - Simplify treatment regimes as much as possible
  - Explain treatment rationale, and negotiate treatment options where possible
- Fertility
  - Most males are infertile
  - IVF may be an option

References

- Therapeutic Guidelines (eTG) – Respiratory (Cystic Fibrosis)
- Cystic Fibrosis Australia website - https://www.cysticfibrosis.org.au/
- AMH
- MIMs
- Micromedex