CYSTIC FIBROSIS MANUAL - CHW

PRACTICE GUIDELINE ©

DOCUMENT SUMMARY/KEY POINTS

- This Manual provides guidance on the management of Cystic Fibrosis patients under the following Chapters:
  - Diagnosis [Chapter 2]
  - Management of newly diagnosed patients [Chapter 3]
  - Respiratory Management [Chapter 4]
  - Gastrointestinal Management [Chapter 5]
  - Nutrition Management [Chapter 6]
  - Psycho-Social Management [Chapter 7]
  - Adolescent Management issues and transitioning to adult care [Chapter 8]
  - CF Outpatient Clinics [Chapter 9]
  - Endocrine Management [Chapter 10]
  - Palliative Care Management [See separate guideline]
  - Cross Infection guidelines [Chapter 12]
  - Other Miscellaneous associated conditions such as musculoskeletal symptoms, sinonasal disease, caring for patients with venous access devices, post procedural pain control for inpatients and exercise testing. [Chapter 13]
  - Research [Chapter 14]
  - Cystic Fibrosis Pharmacopoeia

Acknowledgement to Dr Paul Robinson and team for developing this CF Manual

Approved by:	SCHN Policy, Procedure and Guideline Committee	CHW Drug Committee
Date Effective:	1st April 2015	**Review Period:** 3 years
Team Leader:	Respiratory Staff Specialist	**Area/Dept:** Cystic Fibrosis

CHANGE SUMMARY

- Amalgamated the chapters into one document.
- To make navigating the document sections easier
  - Dashboard map added to give quick access to relevant sections
  - Text converted to bullet point format in main document
- General content updated to be in line with current literature and national/international guidelines.
- The following new protocols have been added:
  - Grey CF protocol
  - Treatment of Staph aureus infection
  - Expanded treatment of MRSA infection
  - Treatment of Haemophilus influenzae infection
  - Expanded treatment of Pseudomonas infection
  - Treatment of Burkholderia cepacia
  - ABPA treatment
  - Initiation of Mannitol treatment
  - Management of Distal intestinal obstruction syndrome (DIOS)
  - Use of Insulin in CF related diabetes
- The following new sections have been added:
  - Antidepressant options in CF (Psycho-Social Management)
  - Oral contraceptive pill options in CF (Adolescent Management)
  - Sinus directed nebulisers (Sinonasal disease)
  - Cystic Fibrosis Pharmacopoeia
- Removed the ED assessment chapter as it was essentially duplicated in other chapters but the information on salt depletion was moved to Miscellaneous and the abdominal pain information was consolidated into the GI chapter.
- **17/02/23**: AMS Pharmacist requested minor change for Bactrim in pharmacopoeia.

READ ACKNOWLEDGEMENT

- All clinical staff who care for patients with Cystic Fibrosis are to read and acknowledge they understand the contents of this Manual.

TABLE OF CONTENTS

1 Overview

- Cystic fibrosis (CF) is the most common life-limiting autosomal recessive genetic disorder in Caucasians. It occurs in approximately 1:3000 live born infants. There are over 2300 patients (59% under age of 18) on the Australian Cystic Fibrosis Database Registry (2003 data), with 60-65 new diagnoses per year.
- It is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) gene on chromosome 7.
    - The gene product functions as a cyclic adenosine monophosphate [cAMP]-regulated chloride channel at the apical surface of epithelial cells.
    - Mutations in this gene result in dysfunctional epithelial transport and subsequent abnormal chloride concentrations across the apical membrane of epithelial cells in the airways, pancreas, intestine, sweat glands and vas deferens.
    - This leads to progressive lung disease, pancreatic dysfunction, elevated sweat electrolytes, and male infertility.
- There is a wide variation in clinical severity.
    - The majority of patients will develop pancreatic insufficiency in early life, and approximately 90% of patients will become pancreatic insufficient during their life.
    - Whilst there is no consistent genotype-phenotype correlation in CF, life expectancy for pancreatic insufficient patients averages around 37 years and for pancreatic sufficient patients the average is approximately 50 years.
    - Although environmental influences may modify clinical disease, additional genetic variation (termed "modifier genes"), also contribute to the expression of the final phenotype.[1]
    - However, factors that are modifiable such as compliance with physiotherapy, pancreatic enzyme replacement therapy (PERT) and diet are the focus of clinical practice, primarily through education and regular clinical review by members of the CF multi-disciplinary team.

Contained in this manual is the key information needed for the management of children with CF based upon current practice at The Children's Hospital at Westmead, Sydney.

The manual, first written in 2002, is regularly updated.

[1] Drumm ML, Konstan MW, Schluchter MD, Handler A, Pace R, Zou F, et al. Genetic modifiers of lung disease in cystic fibrosis. The New England Journal of Medicine. 2005; 353(14):1443-53.

2 Making the Diagnosis of Cystic Fibrosis

- Despite newborn screening, diagnosis of CF may be missed by newborn screening
- Up to 10% of cases present beyond the newborn period, typically with respiratory and gastro-intestinal symptoms.

2.1 Antenatal diagnosis

- The diagnosis of CF is most commonly made in the newborn period.
- Rarely, CF may be suspected during pregnancy by findings of meconium peritonitis during the routine 18-20 week obstetric morphology ultrasound scan.
    - Meconium peritonitis indicates a ruptured bowel with meconium that has leaked into the peritoneum.
- Prenatal testing for CF is offered to couples where both people are confirmed CF carriers.
- Couples planning a pregnancy can discuss the range of pregnancy options available with a genetic counsellor, including prenatal testing and pre-implantation genetic diagnosis (PGD). Prenatal genetic counselling provides detailed information about the options available and facilitating decision-making in keeping with the belief systems of each couple (includes exploration of any religious or cultural considerations).
- Prenatal testing is performed via chorionic villus sampling (CVS) or amniocentesis.
    - CVS is typically performed from 11-13 weeks gestation and amniocentesis is performed from 15-19 weeks gestation. A sample is collected from the chorion (placenta) or amniotic fluid and sent to a prenatal laboratory for processing.
    - Genetic testing indicates whether the fetus **(i)** has both mutations (has CF) **(ii)** has only one of the mutations (is a carrier only) **(iii)** has neither mutation present (not a carrier and does not have CF).
    - Associated risks of miscarriage (approximately 1% and 0.5% respectively). Only performed after careful discussion of the risks and benefits with genetics service.
    - If prenatal testing indicates that the fetus is affected with CF, the woman has the choice of whether or not to continue the pregnancy. This information may also be used to direct delivery of the baby and immediate neonatal management.

2.2 Postnatal

2.2.1 Meconium Ileus

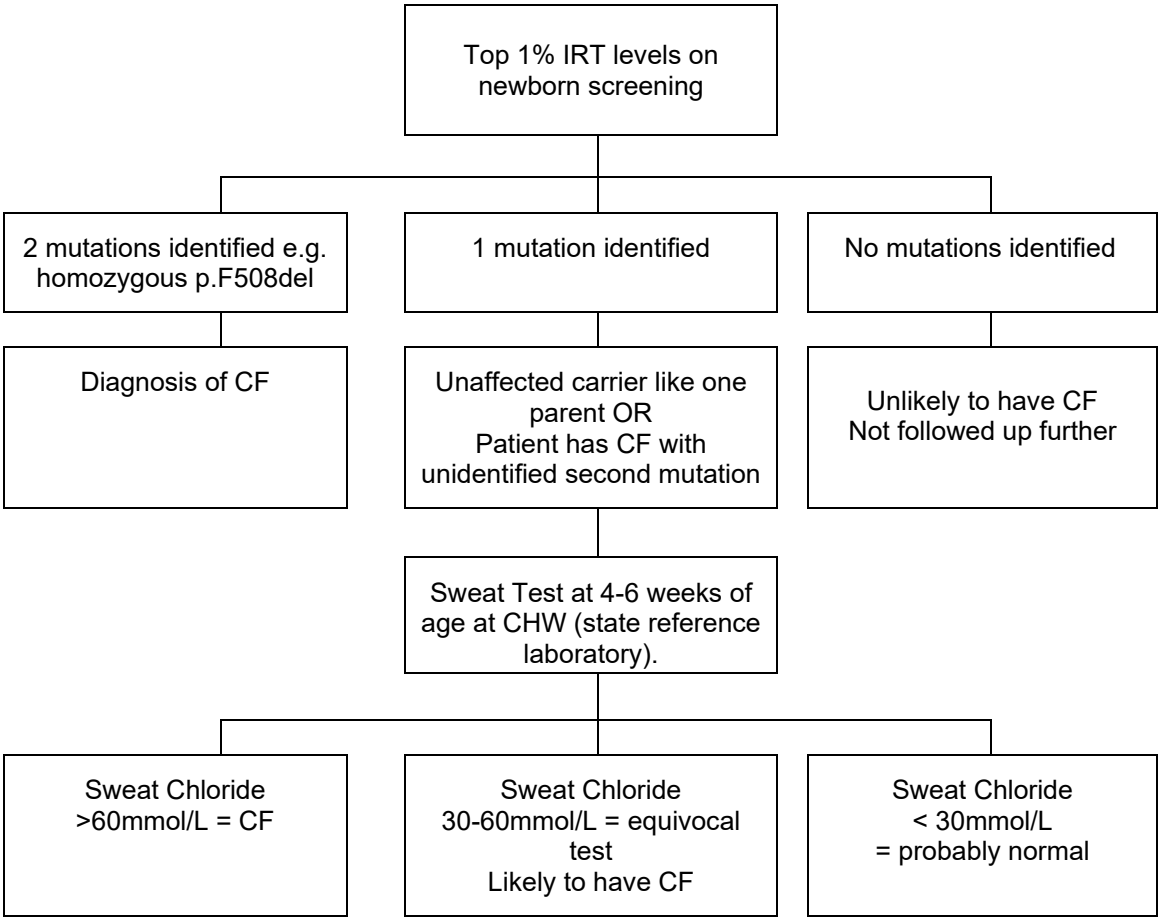
- 15-20% of children with CF present with meconium ileus in the first 48 hours of life.[1]
- Babies develop bowel obstruction due to thick, inspissated stools
    - Manifests with bile stained vomiting and abdominal distension. They fail to pass meconium within 48 hours.
- Initial management:
    - Gut rest with imaging to determine extent of obstruction and distal microcolon size.
    - Surgery may be required to decompress and flush out the bowel. Occasionally temporary colostomies +/- bowel resection are necessary.
    - N-acetylcysteine administration may be useful in this setting.
        - Liver function and electrolytes should be monitored if given. [2,3]
        - Acetylcysteine is given orally, however there is very limited data for the use of acetylcysteine rectally for meconium ileus. The dose, concentration and frequency should be guided by surgeon.
- Meconium ileus may be an early indicator of a more severe phenotype. [4]

2.2.2 Newborn Screening

- The most common way in which the diagnosis of CF is made is through newborn screening.
- All babies in Australia have blood collected at 48 to 72 hours after birth ("Newborn Screen") to test for CF, primary congenital hypothyroidism, galactosaemia, phenylketonuria and with use of tandem mass spectrometry, disorders of amino acids, urea cycle defects, organic acids and fatty acid oxidation.
- To test for CF, the level of immunoreactive trypsinogen (IRT) is measured, a digestive chemical from the pancreas, which is elevated in the blood of most infants with CF.
- Infants with the highest 1% of IRT values for each day are then tested for copies of the three most common CF mutations in the Australasian population (p.F508del, G551D & G542X) as well as the pI507delmutation using blood from the same sample (Figure 2.1).

  The pF508.del mutation accounts for 70% of CF mutations.

Figure 2.1 Outline of Cystic fibrosis Newborn screening at CHW.



- If heterozygous for one of the mutations testing on newborn screening and sweat chloride concentration >30mmol/L then send EDTA blood for the CF mutation panel performed at the Molecular Genetics Laboratory.

  This tests for 39 different CF causing gene mutations. Close to 2000 mutations have been identified in CF to date.
- If a baby is born in a sample period of "high" IRT results, they may not fall into the top 1% of values, and thus be missed by the screening process.
- The number of mutations screened for as part of the newborn screen varies both nationally and internationally.
  - Some countries screen for up to 31 mutations.
- The current genetic mutations tested for in Australasia are shown in the Table 2.1.

Table 2.1 Cystic fibrosis: mutations currently tested for in Australasian screening programmes ***(reproduced with permission from Bridget Wilcken)***

Mutation	NSW	Qld	SA	VIC	WA
p.F508del	+	+	+	+	+
489+1G>T	-	+	-	+	-
1585-1G>A	-	-	-	+	-
3718-2477C>T	-	-	-	+	-
W1282X	-	-	-	+	-
R553X	-	+	+	+	-
R560T	-	-	-	+	-
N1303K	-	+	-	+	-
G542X	+	+	+	+	+
G551D	+	+	+	+	+
V520F	-	+	-	+	-
R117H	-	+	-	-	-
pI507del	+	+	+	+	+

There are 3 possible outcomes of newborn screening:

1. **Two CF mutations identified:** diagnosis of CF.
2. **Only one CF mutation identified:** potential compound heterozygote (i.e. two different mutations causing CF) or carrier (like one of the parents).
    - Referring hospital and nominated doctor notified of result and a sweat test performed at 4-6 weeks of age.
    - CF mutation panel testing to be arranged
3. **No CF mutations identified:** unlikely to have CF (unless he/she had two rare mutations not tested for).
    - Child is not followed up. If later diagnosed with CF, the screening process has missed him/her.

- Reviews of the Victorian screening programme (from 1991-2008, incorporating three different newborn screening protocols) [5,6], has concluded that:
    - Addition of further genetic mutations to pF508.del would not have a significant impact on yield.
    - Recall high IRT babies with no identified CFTR mutation is not justified.
    - Sensitivity rose from 90% to 96% by expanding the mutation panel from pF508.del to 12 mutations. Specificity for both regimens were 99.9%.
- Whilst newborn screening does have some limitations, there is good evidence for a nutritional benefit, although the evidence to support improved respiratory status remains more contentious. [7-10]

2.2.3 Sweat test

- The sweat test measures the concentration of sodium and chloride produced in the skin in response to heat. It is the clinical gold standard test for CF diagnosis.
- It should be performed in a reliable laboratory in a term infant of at least 4 weeks of age (not younger because of the risk of skin burns) or 5kg in weight.
- Most commonly this involves using a biochemistry laboratory in a paediatric teaching hospital or for people living in the country, a large regional centre laboratory that performs the test regularly.
- A minimum of 70gm of sweat is required for a test to be satisfactory. Sweat electrolyte concentration is related to sweat rate.
- At low sweat rates, sweat-electrolyte concentration decreases, and the opportunity for sample evaporation increases.
- The level of sweat chloride is used as the diagnostic measure as follows:
    - *> 60mmol/L*: diagnostic of CF in infancy and early childhood.
    - *30-60mmol/L*: considered equivocal.
        - Approximately 35% of subjects will be diagnosed with formal CF at a later stage (internal audit of results over 15 years, 2013). This is more likely if sweat chloride 40-60mmol/L (60% risk vs. 13% if sweat chloride 30-40mmol/L).
    - *<30mmol/L*: considered normal
- Subjects may have a normal sweat chloride at 4-6 weeks, develop clinical manifestations of CF and have a higher sweat chloride (equivocal or diagnostic range) subsequently. This is seen in pancreatic sufficiency/ milder CF phenotypes.
- Whilst a formal sweat test is done on all babies referred by newborn screening, our laboratory may choose to perform a sweat conductance test on older children, depending on the referral symptoms.
    - Sweat conductance correlates well with sweat chloride[11] and be a useful screening test. It is quicker and easier for laboratory staff. The level of sweat conductance is interpreted as follows:
        - > 80mmol/L: definitely abnormal
        - > 50mmol/L: perform formal sweat test, as this is a “grey zone”.
- A formal sweat chloride should be requested on the form if a sweat conductance is considered inadequate.

2.2.4 Symptoms

- After **newborn screening**, up to 10% of children with CF present with recurrent respiratory tract problems, commonly in association with failure to thrive on the basis of fat malabsorption. [12]
- **Infants and toddlers:**
  - Typically, children with undiagnosed CF will have a persistent moist cough.
  - May be initially thought to have "recurrent bronchiolitis" or asthma.
  - Over time they may develop pancreatic insufficiency with oily, offensive stools (fat malabsorption) and weight loss.
  - Less common presentations include haemolysis due to vitamin E deficiency (fat-soluble vitamin) with pancreatic insufficiency, prolonged neonatal conjugated jaundice and salt depletion in hot weather.
- **Pre-schoolers:**
  - Presence of finger clubbing with ongoing chest signs equals suppurative lung disease such as CF until proven otherwise.
  - Salt depletion with hyponatraemia and dehydration is more common in active outdoor children in hot weather.
  - With prolonged unrecognised malabsorption, albumin levels fall and oedema develops and children may develop rectal prolapse.
- **School-aged children:**
  - Typically thin children labelled as bad asthmatics who are felt to be steroid resistant.
  - Presence of finger clubbing reinforces that the child does not have asthma.
  - With recurrent chest infections, isolation of *Staphylococcus aureus* and/or *Pseudomonas aeruginosa* from sputum together with CXR findings of upper lobe bronchiectasis makes CF likely.
  - Sinusitis and/or the presence of nasal polyps makes CF likely also.
- **Investigations in children suspected of having CF:** If CF is suspected the child should see a paediatrician, who should organise:
  - a sweat test
  - a three-day faecal fat collection to quantitate fat malabsorption
  - blood collection for extended genotyping
  - a sputum specimen if the child has a moist cough and treat with a broad spectrum antibiotic such as amoxycillin + clavulanic acid
  - a stool specimen to look for fat globules.

2.3 "Grey CF"/Equivocal Sweat Tests

- **Defined as** infants identified through newborn screening to have an elevated IRT level, equivocal sweat chloride concentrations (30-40mmol/L) on sweat tests performed at the CHW reference laboratory, and only one CF-causing CFTR mutation.

Management protocol for "Grey CF" subjects:

- Extended genotype testing and respiratory physician review following formal sweat test results (at a reference laboratory).
- Review by other CF team members as clinically indicated.
- 3 monthly follow up during the first year. Follow up in CF clinic if:

  - Symptoms suggestive of cystic fibrosis develop

  - If ongoing follow up by members of the CF team, other than the respiratory physician, are required.
- Sputum samples with intercurrent infections to screen for CF related respiratory bacteria.
- Repeat sweat test at 6 months and 1 year.
- Follow up beyond the first year is dependent on the clinical course during the first year, and at the discretion of the respiratory physician.

2.4 Chapter 2 References

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3 Management of the Newly Diagnosed Patient

3.1 Overview

- A formal assessment over a 3-4 day period is performed on all newly diagnosed patients. Location for this is partly dependent upon geography and family issues.
    - Both inpatient assessment, on Turner Care By Parent unit, or a hospital ward, and outpatient assessment, in the CF Treatment Centre is offered.
- If the diagnosis of CF is made late on symptoms, and not via newborn screening, and the child is unwell at the time of diagnosis with significant respiratory symptoms, then admission to hospital for treatment with intravenous (IV) antibiotic treatment may be necessary
    - Evaluation will be performed during this admission.

Baseline investigations:

- Blood tests:
    - Full Blood count and film
    - Electrolytes, urea and creatinine
    - Liver function tests
    - Serum albumin
    - Coagulation tests
    - Vitamin A and E levels.
    - Bile acids
- Chest X-ray
- Sputum culture - standard pathogens plus also routinely screened for *Burkholderia* (previously *Pseudomonas*) *cepacia*, if diagnosis occurs outside of the NBS period.
- 3 day faecal fat

Instructions on commencing physiotherapy and pancreatic supplements after 3 day fat collection completed are provided if clinically indicated.

The role of the different members of the CF multidisciplinary team for the newly diagnosed patient is shown below.

3.2 Respiratory

- Prophylactic flucloxacillin is given orally for the first year
    - Dose is 45mg/kg/day in 3 divided doses.
    - Dose is adjusted every 3 months, based on weight, using the table below.

Table 3.1: Prophylactic Flucoxacillin dose based on body weight (15mg/kg/dose) through the first year.

If child weighs	Flucloxacillin (250mg/5mL) TDS	Dose givenTDS
3kg or less	0.9mL	45mg
4kg	1.2mL	60mg
5kg	1.5mL	75mg
6kg	1.8mL	90mg
7kg	2.1mL	105mg
8kg	2.4mL	120mg
9kg	2.7mL	135mg
10kg	3.0mL	150mg
11kg	3.3mL	165mg
12kg	3.6mL	180mg

- If symptomatic, treat until symptoms settle with oral flucloxacillin (at full treatment doses), until sputum culture results known.

3.3 Gastrointestinal Tract (GIT)

- All infants with cystic fibrosis need to have a 3-day faecal fat collection in order to determine whether patients are pancreatic sufficient/insufficient.
    - Result takes several weeks before it is available.
- Decision to commence pancreatic enzyme therapy is a clinical one based upon factors including:
    - Child's weight gain
    - Abdominal symptoms
    - Evidence of fat in the stools
    - Documented malabsorption of fat soluble vitamins.
- Infants who present with meconium ileus all have pancreatic insufficiency and commence enzymes from the time enteral feeds are established.
    - Subsequently, a 3-day faecal fat collection off enzymes is considered.
- All children commence multivitamin supplements with added vitamin A and/or E depending upon demonstrated deficiencies.
- Infants may present with jaundice, synthetic liver problems, haemolysis, vomiting and salt depletion.
- A gastroenterologist sees all newly diagnosed infants.

3.4 Nutrition

- Explanation to parents or care givers of the role of dietitian within the CF team
- Assessment of growth and adequacy of breastfeeding/ formula feeding.
    - Growth needs to be corrected if the infant is premature.

- Explanation of basic nutrition and digestion
- Effect of CF on digestion and growth
- Explanation of the faecal fat test and practical considerations for stool collection and recording oral intake
- Possible need for pancreatic enzyme replacement therapy (PERT).
    - Practical demonstration of PERT administration if to commence at completion of faecal fat test.
- Requirement for salt supplementation
- Methods of access to CF dietitian for the parents.
- If patient on formula feeds or breastfeeds with added calories, dietitian to review by telephone on a weekly basis until first outpatient review.

3.5 Physiotherapy

- Explanation to parents or care givers of:
    - The role of physiotherapy and airway clearance in CF.
    - Why physiotherapy is required and how it works.
    - The rationale of the different physiotherapy techniques and how these will change as the child grows and develops
- Demonstration of the appropriate physiotherapy techniques (or airway clearance techniques), after which the parents are taught to do the technique themselves.
    - For an infant this is modified postural drainage and percussion.
- Parents are taught an appropriate home physio program including frequency and timing.
    - This is usually 15-30 mins daily (3-5 minutes per position), depending on the age/size of the baby.
    - If the child develops a productive cough or chest infection, the frequency of physiotherapy is increased to 2-3 times daily.
- Parents are educated on how to look for signs of an exacerbation.
- Physiotherapy should be performed:
    - before or at least 1 hour after a feed to minimise the risk of vomiting and pulmonary aspiration, and is not done while the baby is asleep.
    - at a regular time each day that best suits family life, and methods to aid adherence are also discussed.
- As babies cough spontaneously with secretions, there is no need to stimulate a cough in an asymptomatic baby.[1]
- Encouragement of active play and explanation that exercise will be very important from a young age.
- Review by the physiotherapist at their first clinic appointment to review progress.

3.6 Nursing

- The aim of nursing intervention at diagnosis is to explain the role of the CF nurse consultant as a member of the CF team. This includes:
  - Clinical assessment and advice
  - Education of patient and family
  - Education of other health professionals and carers involved in the life of the child
  - Advocacy
  - Case Management
- The goals at the end of the new diagnosis period are to:
  - Ensure patients and families are provided with a basic understanding of Cystic Fibrosis and treatment plans for their child
  - Ensure families are aware of available supports and how and when to contact them.
- Topics covered during new diagnosis education include:
  - Normal function of the respiratory system
  - Changes related to Cystic Fibrosis
  - Signs and symptoms of an URTI
  - Signs and symptoms of a LRTI
  - Antibiotic use in Cystic Fibrosis including prophylaxis and for treatment
  - Genetics
  - Reproductive system changes
  - Indications for contacting the CF Nurse Consultant
  - Cystic Fibrosis clinic (routine and interval checks)
  - Sputum samples (how, why and when)
  - Chest X Rays
  - Smoking and CF
  - Nebulisers
  - Medications used in CF and how to obtain them
- Often not possible to discuss all these areas of management during a short period.
- Education programs are tailored to the needs and the abilities of individual families. For this reason new diagnosis education may take several months to years to complete.

3.7 Genetics

- All newly diagnosed patients are offered a consultation with the Clinical Genetics Service through the hospital.
    - A Genetics counsellor may see the family initially and an appointment is made to for the family to see a geneticist in the Adult Clinic at Westmead Hospital.
- Consultation will cover further genotyping of the affected child, if needed, parents and can, where appropriate, arrange for extended family screening.
- Screening in future pregnancies will be discussed and the methods of obtaining antenatal diagnosis explained.
- A letter of referral is required.

3.8 Social Work

- At the time of diagnosis of CF, or shortly after, the Social Worker on the CF team will see parents and other family members if necessary.
- The aim of Social Work intervention at this time is as follows:
    - Explanation of the role of the Social Worker on the CF team.
    - Acknowledgment that a diagnosis of CF causes strong emotional reactions for family members.
    - Assistance to process some of the emotional experience and provide understanding and support.
    - Assistance with practicalities associated with hospitalisation and care of a child with CF.
    - Provision of information about support services.
- It is acknowledged that a diagnosis of CF can often precipitate reactions similar to grief, as parents come to terms with the implications this will have for themselves and their child and future pregnancies.
- Dealing with these issues promptly often facilitates adjustment; however the grief reactions of both the child and the family may need ongoing monitoring.
- At the time of diagnosis, the Social Worker aims to ensure that the following areas are covered:
    - Assessment of family's reaction to CF.
    - Assessment of family's composition, roles, relationships.
    - Identification of support systems available to the family.
    - Identification of support organisations.
    - Ability to articulate general information about CF.
    - Fears/hopes/worries.
    - Identification of financial assistance available to CF families.
    - General understanding of the composition of the CF team.

3.9 Community Liaison

- Aim of Community care is to allow children to remain at home whenever possible at the same time ensuring appropriate care and support is available.
- Education is available for any health professional or other agency involved in the care of children with CF.
- Education is routinely provided (as requested) for:
  - Baby health centres
  - Pre schools
  - Schools
  - Community Nurses
  - Base hospitals
- This education is usually provided by the CF CNC however all members of the CF team are available to provide information and support when necessary.
- Resources available to patients and families in the community include but are not limited to:
  - Cystic Fibrosis Treatment Centre
  - Cystic Fibrosis Foundation - New South Wales
  - Cystic Fibrosis Clinical Nurse Consultant
  - General Practitioner / Paediatrician
  - Baby Health Nurse
  - Home Care Services of New South Wales
  - CAPAC (Community and Post-Acute Care) can provide nursing and physiotherapy care in the home for short periods of time, for example:
    - Completing a course of IV antibiotics
    - Support with beginning a new treatment (e.g. insulin, gastrostomy feeds)
    - Refer to Cystic Fibrosis: CAPAC Patient Management Practice Guideline.

Some useful websites are:

- www.cysticfibrosis.org.au
- CF NSW - www.cysticfibrosis.org.au/nsw
- CF Victoria - www.cfv.org.au
- Canada - www.cysticfibrosis.ca
- UK - www.cftrust.org.uk
- North American CF foundation – www.cff.org

4 Respiratory Management

4.1 Physiotherapy

4.1.1 Role of physiotherapy in CF

- CFTR dysfunction causes abnormal ion transport across epithelial surfaces in the airways, causing dehydration of the airway surface liquid layer and mucus.
- This dehydration results in abnormal mucociliary clearance which leads to accumulation of viscous mucus in the airways.[1]
- A vicious cycle then occurs of airway obstruction, atelectasis, chronic infection and inflammation.
- This leads to progressive lung damage.
- The goals of physiotherapy are to: [2]
    - Optimise airway clearance to reduce the risk of obstruction, infection and inflammation, thereby improving ventilation, gas exchange and slowing down the progression of lung damage.
    - Optimise exercise capacity, maintain muscle strength, length, chest wall mobility and bone mineral density.

4.1.2 Role of the Physiotherapist in Outpatient Clinics

- Assess respiratory status and design/review individualised home programs to optimise airway clearance, in collaboration with children and their families.
    - Appropriate airway clearance techniques (ACT), dosage and frequency are prescribed and correct technique taught.
- Assess inhalation therapy programs and optimise this in liaison with CF team.
- Assess and ensure optimal inhalation therapy technique, equipment and cleaning.
- Modify airway clearance programs based on radiological, microbiological and pulmonary function outcomes.
- Advocate the importance of exercise from infancy, encouraging age and disease appropriate activities / exercise programs. This will include education on safe exercise in children with co-morbidities and complications.
- Assess exercise capacity.
- Assess and treat musculoskeletal problems and urinary incontinence.
- Continually educate children and their families on the disease and its treatment.
- Assess treatment adherence and work with the child/family to improve adherence.
- Tailor individual physio programs to be as effective and time-efficient as possible.
- Physiotherapists aim to review patients at every clinic visit as necessary, and perform a comprehensive review once a year at their annual review.

1st outpatient appointment to 12 months

- The family is routinely reviewed at their first clinic visit and on subsequent visits in the first year to provide continuing support and education.
- Physiotherapy techniques are revised and timing and tolerance reviewed.
- As the child grows, vibrations are added to the percussion routine, and active play is encouraged including normal developmental play and bouncing on a swiss ball.
- If the child is struggling to tolerate the standard program, other techniques can be trialled including infant PEP and bouncing on a swiss ball with assisted huffing / assisted autogenic drainage. [3]
- If an inhaled therapy is thought to be beneficial to optimise airway clearance at any age, the physiotherapist will liaise with the CF team and may carry out a trial of hypertonic saline.

12 months to 2 years

- Percussion and vibrations in the modified postural drainage positions continues as the standard physio program. Time spent in each position is increased.
- The child is encouraged to mimic coughing and when able to cough during the treatment to clear loosened secretions.
- There may be a need to advise the family to purchase a physio table due to the child's increasing size.
- Blowing activities are introduced, and at about 2 years bubble blowing in the bath is encouraged, to begin learning to blow against a resistance.
- Exercise options are progressed and the importance of physical activity re-emphasised.

3 to 4 years

- Children are taught to huff using huff tubing, mirrors or tissues for feedback.
- Huffing encouraged to be incorporated into active play / exercise and airway clearance sessions to optimise clearance.
- Bubble PEP will also be introduced and exercise options are progressed including swimming, toddler trampolines and kindy gym.
- A more structured physio routine is encouraged of once daily ACT and a once daily exercise session (with huffs and coughs incorporated).
- Reminder is given that if the child is unwell this should be increased.

School age

- When proficient at bubble PEP and huffing, PEP mask therapy is introduced.
- Huffing from low, mid and high lung volumes are taught to optimise clearance, and breathing exercises e.g. The Active Cycle of Breathing Technique (ACBT) may also be introduced. Can be done during a nebuliser to improve deposition.
- If the child uses hypertonic saline and is proficient at PEP they may trial combined PEP and hypertonic saline therapy.
- High frequency chest wall oscillation may be an appropriate treatment option in certain situations but this should be assessed on an individual basis, with the significant cost

being taken into account. PEP remains the preferred approach, with superior results in a recent direct comparison study.[4]

- Singing and wind instruments are encouraged as a good form of exercise for the respiratory muscles and can aid in airway clearance.
- Team sports / group exercise is encouraged to enhance fun, socialising and to aid adherence.
- Exercise programs are encouraged to have a mixture of aerobic exercise, strengthening, weight-bearing exercise and activities which strengthen arm and chest muscles and maintain good chest movement to prevent problems with posture as they get older.
- Assessment and treatment of musculoskeletal problems and urinary incontinence will be done at annual review.
- Annual assessment of exercise capacity using the Modified Shuttle Walk Test.[5]
- Inhalation therapy review including technique, timing and equipment. If the need for introduction of an inhaled therapy to aid airway clearance is observed, this should be highlighted and discussed with their respiratory consultant.

Adolescents

- Adherence to physiotherapy can be very difficult during the adolescent years.
- Physiotherapists will work with individual adolescents and families to come up with the most effective and time efficient physio program.
- Other ACT alternatives may be trialled including oscillating PEP (Flutter or Acapella), Autogenic Drainage (AD) or a program based on exercise incorporating huffs/coughs.
- Goal setting and behavioural interventions such as motivational interviewing may be used to improve treatment adherence.

Co-morbidities

- Physiotherapists will modify treatment programs according to any co-morbidities and complications. These are covered in individual sections of the manual.

4.1.3 Role of the physiotherapist for Inpatients

- Assessment of each patient to develop the most appropriate airway clearance and exercise program for them during the admission. They will continually re-assess the patient's progress and modify their program as required.

Objectives

- Assessment of the patient's respiratory status, airway clearance and exercise requirements and their response to intervention.
- Optimise airway clearance (including inhalation therapy) and exercise capacity.
- Assess and treat musculoskeletal problems.
- Continual education.

Admission for Acute Chest Infection or "Tune Up"

- **Assessment**
  - All patients are assessed by a physiotherapist on the day of admission regardless of reason for admission. Based on assessment, an individualised physiotherapy program is designed.
  - A sputum sample is obtained and sent on day one of admission.
  - The Modified Shuttle Walking Test[5] should be completed on admission and discharge (when age appropriate). If the patient is unable to complete the Shuttle Test, a six minute walk test may be appropriate.[2]
- **Treatment**
  - Minimum of two physiotherapy sessions per day, routinely an airway clearance session on the ward in the morning, and an exercise session in the gym in the afternoon. This is at the discretion of the physiotherapist.
  - Gym sessions should include a mixture of exercise types including aerobic, anaerobic, stretching, strengthening, weight-bearing / high impact exercise as well as exercises for chest mobility and posture as appropriate.
  - Supplemental oxygen or non-invasive ventilation may be used during exercise as required.
  - IV lines should be capped off if possible.
  - **After hours:**
    - Evening / overnight treatment is not routine but may be indicated for patients with increased airway clearance requirements, acute deterioration or post op.
    - Saturdays, Sundays and Public Holidays - all patients should continue to receive two sessions of physiotherapy per day.
  - If parents wish to take children on gate pass they are responsible for performing any physiotherapy sessions which are missed.
  - If a patient is independent and reliable with their physiotherapy they may be allowed to do some sessions independently.

Liaison with CF Team during admissions

- Inpatients are discussed at the respiratory pre-ward rounds on a Monday and Friday and at the Tuesday CF team meetings.
- Physiotherapists will also continually liaise with members of the CF team as required in regards to progress, initiation of new inhaled therapies, complications, timetabling of complex patients etc.

Admissions for Non-respiratory Reasons

- Patients may be admitted for gastrointestinal or nutritional reasons e.g. DIOS.
- These patients will be assessed as usual, however if they are well from a respiratory perspective they will only be seen once daily by the physiotherapist.

Admission for Surgical Procedures

Prior to abdominal surgery and insertion of Port-a-cath devices, patients may be admitted for a period of IV antibiotics and physiotherapy.

- Patients will be reviewed post op the day of surgery, if they return to the ward late the evening physio will see them.
- Adequate pain relief must be arranged prior to treatment.
- Physio will determine the most appropriate airway clearance routine depending on the surgical procedure performed, the patient's pain levels etc. and will progress as appropriate.
- Early mobilisation as soon as appropriate.

After liver biopsy or percutaneous trans-hepatic cholangiogram,

- Position for 4 hours on the right side with bed rest for 24 hours.
- Modified postural drainage and percussion are contraindicated in the first 4 hours after both of these procedures.
- GENTLE percussion and modified postural drainage may be done after that, for the first 24 hours post-op.

Admission for sinus surgery

- Patients can continue using PEP therapy but the mask must be replaced with a mouthpiece.
- Continue using a mouthpiece until the ENT surgeon clears them for use of the mask, usually after 4 – 6 weeks.

4.2 Stepwise Treatment of Respiratory Exacerbations

Assessment of respiratory status incudes:

- Cough,
- Sputum colour and amount
- Exercise tolerance
- Signs of respiratory distress
- Auscultation - new or increased crackles, wheeze
- Spirometry
- Oxygen saturations.

4.2.1 Minor exacerbation

- Lesser changes in respiratory status are apparent. FEV_1 fall typically <10% predicted.[6]
- Systemic changes are usually absent.
- Admission to hospital is usually not necessary.
- Management of minor exacerbations:
  - Review old notes.
  - Check sputum.
  - Give oral antibiotic, e.g. amoxycillin & clavulanic acid, if possible based on recent sputum, until symptoms settle.
  - Increase physiotherapy.
  - Arrange review: CF community nurse/CF Clinic/LMO, if not settling in 5–7 days.
  - Depending on sputum result and progress, change oral antibiotics or add inhaled tobramycin or oral ciprofloxacin (if colonised with *P. aeruginosa*).

4.2.2 Major exacerbation

- A significant deterioration in respiratory status combined with systemic symptoms and signs (e.g. high fever, anorexia, weight loss) has developed. FEV_1 fall typically >10% predicted.[6]
- Management of major exacerbations:
  - Admit with antibiotic choice based on recent sputum culture results and sensitivities.
  - Inform CF team (Dietitian, Social Worker, Physiotherapist, Consultant).
  - IV antibiotics and insertion of long line (unless port-a-cath in situ)
  - Discharge when respiratory symptoms, especially cough, sputum production, exercise tolerance, lung function, Oxygen (O_2) saturation and weight show considerable improvement.

Table 4.1 Treatment of Respiratory exacerbation without known *P. aeruginosa* & MRSA infection

Drug	Dosage	Route	Frequency
Cefotaxime	50mg/kg/dose (max 2g)	IV	TDS
Consider addition of:			
Flucloxacillin	50mg/kg/dose (max 2g)	IV	QID

  - Second line: Piperacillin-Tazobactam (Tazocin) as a single agent
  - For patients with peripheral cannulas or midlines, consider slower rate of infusion or oral administration of flucloxacillin.

4.3 Indications for Hospital Admission for Lung Disease

Indications for admission:

- Major respiratory exacerbations (section 4.2.2 above).
- Minor exacerbations, not responding to home (oral or inhalational) therapy (section 4.2.1).
- Pre-arranged "tune-ups" for those with established suppurative lung disease to delay decline.
- First isolation of *P. aeruginosa* not responding to outpatient directed therapy or associated with significant respiratory symptoms (section 4.4.4)
- Fresh haemoptysis (section 4.10).
- Pneumothorax (section 4.11).
- Acute abdominal pain (section 10.2).

4.4 Antibiotic Management of Pathogen Colonisation

- Treatment of recurrent or persistent bacterial infection in the lung with appropriate antibiotics is a corner stone of respiratory management in CF.
- *Staphylococcus aureus* and *Pseudomonas aeruginosa* have a particular tendency to colonise the CF lung.
- Other bacteria such as *Haemophilus influenzae* (in 5%), *E. coli* (in infancy) and *Klebsiella* are also found but their presence tends to be intermittent.
- Chronic colonisation is defined as either of:
    - Three positive sputums in one year
    - Mucoid *P. aeruginosa* phenotype
    - On chronic anti-pseudomonal nebulised antibiotic therapy
- Once the CF lung is chronically colonised with an organism it is extremely difficult to eradicate completely and the goals of therapy at that stage are usually suppression or at best temporary reduction in organisms with antibiotic therapy.
- In the early stages of colonisation (particularly with *Pseudomonas*) when the organism is present in small numbers or only intermittently, it is possible that aggressive therapy may delay the onset of chronic colonisation and potentially slow the progression of lung disease.
- The main stays of management of bacterial colonisation are regular accurate clinical assessment of respiratory and general status and regular surveillance of sputum (three monthly as a minimum) to determine the prevalent bacteria.

4.4.1 *Haemophilus influenzae*

- Commonly encountered organism, especially in CF subjects early in childhood.[7,8]
- Evidence supports a pathogenic and pro-inflammatory role in the CF airway.[9]

Treatment Protocol for *Haemophilus influenzae* *(See Pharmacopoeia for doses)*:

First growth

- *Well child (clinical judgment), home therapy:* oral amoxycillin & clavulanic acid (Augmentin Duo) for 2-3 weeks. If fully sensitive and a pure growth, oral amoxicillin should be strongly considered.
- *Unwell child (clinical judgment), In patient admission:* IV antibiotics for 14 days (decision based on sensitivities, if available). For empiric treatment, 1st line antibiotics are cefotaxime and flucloxacillin

Re-growth

- *Well child (clinical judgment), home therapy:*
  - ❖ *Less than six months from first growth:* oral amoxycillin & clavulanic acid (Augmentin Duo) for 28 days. If fully sensitive and a pure growth, oral amoxicillin should be strongly considered.
  - ❖ *Greater than six months from first growth:* Treat as for first growth (above)
  - ❖ *Further re-growth within six months:* 2nd line agent eg. clarithromycin for 28 days (or alternative antibiotic based on sensitivities)
- *Unwell child (clinical judgment), In patient admission:* IV antibiotics for 14 days (decision based on sensitivities, if available, and previous clinical response) For empiric treatment, 1st line antibiotics are cefotaxime or tazocin (flucloxacillin if known to have *Staph aureus*).

Chronic colonisation:

- In the following children consider continuous amoxycillin & clavulanic acid (Augmentin Duo) at treatment dose ideally over winter months but longer if clinical symptoms develop:
  - ❖ Children with chronic *H. influenzae* colonisation develop respiratory symptoms when anti-Haemophilus antibiotics are ceased.
  - ❖ Children with frequent (> 3 episodes per year) or recurring exacerbations
- If fully sensitive and a pure growth, oral amoxicillin should be strongly considered.

Persistence of respiratory symptoms despite continuous anti-Haemophilus prophylaxis also indicates the need to search for other organisms (especially P. aeruginosa)

4.4.2 *Staphylococcus aureus Colonisation*

- *S. aureus* is the usual initial organism found in the CF lung, and by the age of one year approximately 20-25% of children will have *S. aureus* in their sputum.
- Thereafter, colonisation rate continues at around 30-35%.
- In some children this is asymptomatic, whereas in others recurrent persistent symptoms may occur and severe lung disease can result.
- Regular sputum surveillance will ensure an awareness of this organism.

Treatment – Early Years

- Continuous prophylactic anti-staphylococcal cover (flucloxacillin or occasionally erythromycin) is routinely used for all infants in the first year of life irrespective of the presence of the organism.
- The antibiotic is usually ceased in the second year of life. This issue is also contentious. There is some concern over increased rates of subsequent *Pseudomonas* colonisation, but no definitive data exists.[9-11]
- There is no evidence that continuous antibiotic prophylaxis is more likely to lead to the colonisation of the respiratory tract with methicillin-resistant *S. aureus* (MRSA)
- By the end of the first year, it will be apparent in most circumstances whether the child is prone to more persistent *S. aureus* colonisation.

Treatment Protocol for *S. aureus* (non-MRSA) *(See Pharmacopoeia for doses)*

First growth

- *Well child (clinical judgment), outpatient therapy:* oral flucloxacillin for 2 weeks.Consider oral Keflex as a better tasting alternative.
- *Unwell child (clinical judgment) inpatient admission:* IV antibiotics for 14 days (decision based on sensitivities, if available). For empiric treatment, 1st line antibiotics are flucloxacillin +/- cefotaxime (if other sensitive organisms present). Cefotaxime will not add additional Staph aureus cover to flucloxacillin.

Re-growth

- *Well child (clinical judgment), home therapy*
  - ❖ *Less than six months from first growth:* Oral flucloxacillin for 3 weeks. Consider oral Keflex as a better tasting alternative
  - ❖ *Greater than six months from first growth:* Treat as for a first growth (above)
  - ❖ *Further re-growth within six months:* Two anti-staphylococcal antibiotics for 28 days (discuss choice with Microbiology based on sensitivity profile.
- *Unwell child (clinical judgment), Inpatient admission:* IV antibiotics for 14 days (decision based on sensitivities, if available). For empiric treatment, 1st line antibiotics are flucloxacillin +/- cefotaxime (if other sensitive organisms present). Cefotaxime will not add additional staph aureus cover to flucloxacillin. Other options include Beta-lactam plus nebulised aminoglycoside.

Chronic Colonisation

Consider continuous flucloxacillin (or other sensitive antibiotic at treatment dose) on a long term basis in:

- Children with chronic *S. aureus* colonisation develop respiratory symptoms whenever anti-staphylococcal antibiotics are ceased.
- Children with frequent (> 3 episodes per year) or recurring exacerbations driven by *S. aureus*

Persistence of respiratory symptoms despite continuous anti-staphylococcal prophylaxis also indicates the need to search for other organisms (especially P. aeruginosa).

4.4.3 Methicillin-Resistant Staphylococcus aureus (MRSA)

- MRSA rates at CHW have risen in recent years (approximately 10% of the clinic). [Unclear whether this is a "true" increase or whether it relates to the advances in detection that have occurred].
- Whether MRSA is a significant cause of lung disease in CF children is an ongoing debate, and definitive studies are lacking. [12]
    - Increasing body of evidence suggesting pathogenicity [13] and a detrimental effect on subsequent lung function decline.
    - Future prospective studies will hopefully provide definitive answers.
- Recommended approach is to **attempt MRSA eradication following isolation**.
- Other important implications of MRSA status:
    - Risk of cross infection (see Chapter 12)
    - Relative or absolute contraindication for lung transplant.

Treatment Protocol for methicillin-resistant *S. aureus* (MRSA) *(See Pharmacopoeia)*

1st line treatment:

- 2 week course of **one** of the following combinations (based on sensitivities):

❖ Oral rifampicin *and* fusidate sodium
If not tolerating fusidate sodium then consider cotrimoxazole or clindamycin (after discussion with Microbiology regarding sensitivity profile).

- ***plus*** Nasal mupirocin and cutaneous triclosan body wash.
- Additional information environmental cleaning measures can be found at: http://www.asid.net.au/hicsigwiki/index.php?title=Main_Page
- Repeat sputum culture, skin and nasal swabs should be taken following completion of the above treatment course.

2nd line treatment:

- Repeat treatment as outlined above (again based on sensitivities) *plus*
- other family members screened for MRSA airway carriage using nasal swabs

If positive, commence decolonisation protocol of nasal mupirocin and cutaneous triclosan body wash.

3rd line treatment:

Consider:

- 1 month of nebulised tobramycin or gentamicin administered via face mask.

❖ To date paediatric hospital based MRSA isolates have been aminoglycoside sensitive, in contrast to those within adult hospitals.

- Longer course of oral antibiotics (as outlined in the first line treatment section) given for 3-6 months.
- Consider concurrent use of dilute bleach baths which have been successfully used in atopic dermatitis patients with good success[14]. Contact Infectious diseases for guidance on patient suitability. Contact Dermatology for administration protocol.

Given the lack of strong current evidence to support eradication, decisions in patients to proceed to 3rd line therapies should involve careful evaluation of the likely organism pathogenicity in that patient, and discussed with a microbiologist.

4.4.4 Pseudomonas aeruginosa

- Most important organism to chronically colonise the CF lung and is the cause of the majority of lung disease in CF.
- Initial colonisation usually occurs at some time later than *S. aureus*.
    - By the age of 5 years: approximately 30% colonised, 60% by 10 years.
    - In the early stages of colonisation, organism exists in non-mucoid form.
        - Eradication, or delayed colonisation is possible with therapy.
    - Once mucoid form predominates, eradication virtually impossible.
- Early colonisation may be asymptomatic, but typically leads to increased symptoms (usually cough) which may be low grade or persistent.
    - Regular sputum surveillance may be effective in detecting early colonisation but in the symptomatic non-sputum producing child who has negative sputum culture a bronchoscopy may be necessary to confirm.

Eradication Treatment Protocol of *P. aeruginosa* isolation
(See Pharmacopoeia for doses)

***Aim**: aggressively eradicate or at least delay early onset of pseudomonas colonisation in the CF lung.*

Initial positive culture:

- Well child or asymptomatic (clinical judgement):

- Nebulised tobramycin for 1 month
- Oral ciprofloxacin for 3 weeks

If cleared then future intermittent isolation is managed with similar repeat courses of inhaled tobramycin and oral ciprofloxacin.

- Unwell child or significant symptoms (clinical judgement): 2 week course of IV antibiotics immediately indicated. See Table 4.2 & Table 4.3.

Persistence after Initial Treatment:

- Well child or asymptomatic (clinical judgement):

- Repeat course of nebulised tobramycin for 1 month plus oral ciprofloxacin for 3 weeks
- Failure to eradicate: Admit to hospital for 2 weeks IV therapy. Two antibiotics are chosen due to their synergistic action. See Table 4.2 & Table 4.3.

- Unwell child or significant symptoms (clinical judgement): 2 week course of IV antibiotics immediately indicated. See Table 4.2 & Table 4.3.

For treatment, two antibiotics are chosen due to their synergistic action towards Pseudomonas. See Table 4.2 (below) for first line management.

Table 4.2 Management of exacerbation with known *P. aeruginosa* infection

Drug	Dosage	Route	Frequency
Tobramycin	10mg/kg/dose Then adjusted as per AUC	IV	Daily
plus			
Timentin (Ticarcillin and clavulanic acid)	100-150mg/kg/dose (max 6g)	IV	QID

2nd line: Tobramycin *in combination with* one of those listed in Table 4.3. Used only after discussion with the consultant when the patient has multi-resistant Pseudomonas or poor clinical response to the above therapy.

Table 4.3 Second and third line management of *P. aeruginosa* infection

Non-aminoglycoside anti-pseudomonal agents 2nd line: Tobramycin *in combination with* one of those listed below. Used only after discussion with the consultant when the patient has multi-resistant Pseudomonas or poor clinical response to the 1st line therapy. 3rd line: Two non-aminoglycosides would be considered from those listed below if 1st and 2nd line therapies are ineffective.			
Drug	**Dosage**	**Route**	**Frequency**
Tazocin (piperacillin and tazobactam)	100-150 mg/kg (Max 4g)	IV	QID
Ceftazidime	50mg/kg/dose (max 2g)	IV	TDS
Meropenem	40mg/kg/dose (max 2g)	IV	TDS
Cefepime	50 mg/kg (max 2g)	IV	TDS
Imipenem and cilastatin	25mg/kg/dose (max 1g)	IV	QID
Aztreonam	50mg/kg/dose (max 2g)	IV	TDS
Ciprofloxacin	10-15mg/kg (max 400mg)	IV	TDS

Treatment Protocol of chronic *P. aeruginosa* colonisation
(See Pharmacopoeia for doses)

- Once chronically colonised, the approach changes to acceptance rather than aggressive intervention.
- Chronic colonisation defined as 3 consecutive sputum's positive for pseudomonas or persistence after IV antibiotic course.
- Management strategy depends on pattern of clinical symptoms.

Intermittent, but not daily symptoms with chronic colonisation:

- Exacerbations treated with 1 month nebulised tobramycin plus 2 weeks oral ciprofloxacin. Treatment ceased following resolution of the exacerbation.

Daily symptoms and chronic colonisation:

For prophylaxis against P. aeruginosa (at home) inhaled tobramycin is treatment of choice. To reduce the risk of resistance, administer tobramycin every second month (i.e month on, month off).

Where resistance to tobramycin develops, and the clinical benefit is not apparent, other nebulised medications can be considered, such as:

- ❖ Switching to a second line nebulised antibiotic eg colistin, aztreonam or ceftazidime
- ❖ Addition of a second line antibiotic during the month off tobramycin

Dry powder inhaled antibiotics eg Tobi Podhaler should be considered in patients with adequate technique for administration

Exacerbations:

- Exacerbations treated with additional oral ciprofloxacin for 2 weeks.
- Recurrent exacerbations or chronic ill health despite above require admissions for 2-3 weeks of IV anti-pseudomonal antibiotics. Nebulised antibiotics are discontinued during IV antibiotic courses.
- Frequency of admission depends on the clinical state and well-being of the patient, decided by frequent assessment.

IV Anti-Pseudomonas Therapy "Tune Ups"

- Patients with long standing *Pseudomonas* colonisation will eventually require elective regular IV antibiotic courses directed against Pseudomonas to maintain their clinical condition.
- Regular IV courses allow for easier forward planning, and may maintain general well-being, weight gain and pulmonary function.
- Administered as inpatient therapy or at home via CAPAC.
- With prolonged inhaled therapy and repeated IV antibiotic admissions, sputum sensitivity to *Pseudomonas* will often change, with the development of multi-resistant strains of both mucoid and non-mucoid species.
- Treatment should be with a combination of at least two antibiotics; one of which should be an aminoglycoside.

- Clinical response is as important as the microbiological report.
- Sputum culture should be sent on admission. Monitor results and antibiotic sensitivities during admission as a change from sensitive to resistant may indicate the need to change IV therapy particularly if associated with poor clinical response.

- Multiple combination sensitivity testing (MCT)
  - Reserved for cases of multi-resistant pseudomonas with lack of clinical response to standard 1st or 2nd line anti-pseudomonal antibiotics.
  - Routine use is a source of debate.[15] It has not been shown to improve outcomes when on pre-admission surveillance sputums[16], however, the role of MCT in patients unresponsive first and/or second line antibiotics was not investigated in this study.

Clonal Testing for Pseudomonas Strains

Requested when clinically indicted:

- Newly acquired strain of *P. aeruginosa* (either mucoid or non-muciod) and has a multi-resistance pattern, contrasting with the normal non-mucoid sensitive patterns of most strains.
- Particularly if this coincides with more rapid decline in clinical status.

4.4.5 Burkholderia cepacia Complex

- Consists of nine species, with *B. cenocepacia* and *B. multivorans* the most common.[17]
- Infection affects CF patients in different ways.
  - May be asymptomatic
  - Can lead to a slow decline in lung function.
  - Rare but serious "Cepacia Syndrome". Associated with *B. cenocepacia*.
    - Characterised by accelerated and often fatal deterioration in lung function with fever, necrotising pneumonia +/- septicaemia.
- Presents therapeutic problems, as it is generally resistant to the beta-lactams, fluoro-quinolones and aminoglycosides.
- Patients with poorer spirometry at the time of infection appear to be at greatest risk of Cepacia Syndrome but survival cannot be predicted from age, sex, duration of colonisation or antibody response.
- Other patients have apparent intermittent colonisation with *B. cepacia* and eventually clear it without treatment.
- *B. cepacia* colonisation associated with a transition from mucoid to non-mucoid form (with increased resistance to oxidative stress).[18]
- No randomised control trials to date to guide eradication therapy decisions.[19]

Treatment Protocol of Burkholderia species *(See Pharmacopoeia for doses)*

Initial positive culture:

- Confirm with repeat sputum culture, if 2nd sputum culture negative, confirm negative on BAL.
- *B. cepacia* genomovar testing should be performed for all confirmed positive cultures.
- *Well child or asymptomatic (clinical judgement):*
  - ❖ Potential for outpatient treatment based on sensitivities. [*Note: this organism is inherently resistant to aminoglycosides*]
  - ❖ *If cleared* on repeat sputum culture then confirm with BAL sampling
  - ❖ *If persists* then admit for 2 week IV antibiotic course using two antibiotics based on sensitivities. Referral to CAPAC for completion of course may be indicated if clinically well.
- *Unwell child or significant symptoms (clinical judgement):*
- Admission for IV antibiotics is immediately indicated with a minimum duration for 2 weeks. Two antibiotics should be chosen based on antibiotic sensitivities.
- On discharge, give one month of outpatient treatment based on sensitivities

If remains positive despite attempted eradication:

- ❖ Commence suitable oral/nebulised antibiotics at treatment doses and continue until negative for 12 months then trial off to see if reisolates (if clinical status permits).
- ❖ Cotrimoxazole (Bactrim™) is typically used for this purpose.
- Clearance or eradication defined as 2 consecutive clear sputum cultures and a one year gap from the last positive culture.

Another major concern with *B. cepacia* is cross infection.

- Direct and indirect transmission appears to be considerably greater than that observed with *P. aeruginosa* or other CF pathogens.
- Strains of *B. cepacia* have been reported to spread in epidemic fashion within individual CF centre populations.[20]
- There is evidence that social contact outside of hospital is important in the spread of the epidemic strain within and between clinics.
- Strict guidelines regarding cross infection in *B. cepacia* both in the outpatient and inpatient settings are enforced at CHW (see Chapter 12).
- The prevalence of *B. cepacia* in our CF Clinic at CHW is very low (2-3%).

Precautions

- Isolate all children who are colonised with *B. cepacia* as outpatients and inpatients.
- As with all CF outpatients, members of the CF team visit the child in that room.
- Lung function is obtained at the end of the clinic after other CF patients have left.
- Patients with *B. cepacia* are fully informed as to the necessity to maintain strict cross infection routines.
- On admission to hospital they are cared for in isolation cubicles as per MRSA and do not mix with other children either in the ward at hospital, in school or during physiotherapy.
- Social contacts with CF should also be informed of *B. cepacia* status of friends.
- Once clear, allowed to mingle with the general CF population.

4.4.6 Non-tuberculous mycobacteria (NTM)

- NTM should be considered in the CF patient who is clinically or radiologically deteriorating and has not improved with standard therapy.
- The impact of NTM on the natural history of CF remains unclear.
- NTM has emerged as a lung pathogen, as the lifespan of patients with CF has increased.
- In a large multicentre US study, in which over 10% of the US CF population were enrolled, the overall prevalence of NTM was 13%, with the majority of the isolates being *Mycobacterium avium* complex (MAC).[21]
    - Strong association with age and an association with preserved lung function independent of age.
    - Positive patients tended to have less *P. aeruginosa* and more *S. aureus*.
    - Over 15 months of follow up the authors described:
        - a non-significant trend for steeper rate of decline in those with NTM meeting ATS microbiologic criteria for disease (20% of NTM positive patients, see below for criteria).
        - Progression of high resolution CT changes was seen in patients from whom NTM organisms were repeatedly recovered.
- Serial sputums (at least 3) for AFB stain and culture are essential for diagnosis.
- Skin testing has not been shown to be diagnostic in NTM infections, due to cross – reactivity and false positives due to environmental exposure without true disease (Applies to both standard PPD and specific NTM antigen skin testing).
- Differentiation between colonisation, innocuous infection, and serious disease is very difficult.

ATS criteria for diagnosis of NTM pulmonary disease [22]

Both clinical and microbiologic criteria must be met.

Clinical:

- Pulmonary symptoms, nodular or cavitary opacities on CXR, or an HRCT scan that shows multifocal bronchiectasis with multiple small nodules, and
- Appropriate exclusion of other diagnoses.

Microbiologic:

- Positive culture results from ≥ 2 separate expectorated sputum samples. (If the results from the initial sputum samples are non-diagnostic, consider repeat sputum AFB smears and cultures) **OR**
- Positive culture results from ≥ 1 bronchial wash or lavage, **OR**
- Transbronchial or other lung biopsy with:
    - ❖ mycobacterial histopathologic features (granulomatous inflammation or AFB) and positive culture for NTM **OR**
    - ❖ biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and ≥ 1 sputum or bronchial washings that are culture positive for NTM.

- Consultation with ID team is encouraged when NTM are recovered that are either infrequently encountered or that usually represent environmental contamination.
- Patients with suspected NTM lung disease who do not meet diagnostic criteria should be followed until diagnosis is firmly established or excluded.
- Diagnosis of NTM lung disease does not, per se, necessitate institution of therapy. Decision based on potential risks and benefits of therapy for individual patients

Treatment regimen is decided after consultation with Infectious Diseases and the 2007 Official ATS/IDSA statement on NTM disease (for specific treatment recommendations).[22]

- Treatment typically involves:
    - Multiple drug regimen:
        - Typically includes rifampicin, ethambutol, and either clarithromycin or azithromycin.
        - IV agents (e.g. amikacin, tigecycline) may be indicated for more severe disease.
    - Prolonged duration of treatment: typically for at least 12 months after cultures become negative.
    - Monitoring for signs of drug toxicity.
- Treatment efficacy depends on the NTM species isolated.
    - High eradication rates have been reported with *Mycobacterium avium* complex (MAC): 10/11 (all but one MAC) cleared with prolonged treatment for 2 years (including all 8 paediatric patients).[23] This is much better than literature rates for non-CF patients with NTM (only 35-40%).
- Currently, we do not screen our CF population, due to the difficulties outlined in interpretation of positive results.
- The following are **indications for sputum screening for NTM**:
    - Clinical or radiological deterioration and no improvement with standard therapy, particularly if their predominant lung pathogen is *S. aureus*.
    - Azithromycin use in patients with CF is associated with increased infection with nontuberculous mycobacteria (NTM). Sputum screening for NTM is required prior to commencement of Azithromycin therapy.
        - Ideally a separate sample of at least 2mL (enough to cover the bottom of a sputum collection container) should be sent prior to starting of azithromycin AND every six months whilst on treatment.

4.5 Anti-Inflammatory Medications in CF

Immune-mediated airway inflammation as a result of host response to airway colonisation with bacteria is an important factor in the pathogenesis of lung disease in patients with CF. There has therefore been considerable interest in the role of anti-inflammatory medications in CF.

4.5.1 Oral Corticosteroids (OCS)

- OCS slow progression of lung disease when used regularly over several years.
- However, particularly at higher doses, OCS often produce significant adverse events e.g. impaired glucose tolerance/diabetes, cataracts, growth retardation.[24]
- OCS are therefore currently recommended for short term use in:
  - Co-existent asthma
  - Allergic Bronchopulmonary Aspergillosis (ABPA)
  - Where a significant inflammatory component to illness is suspected.
- Prednisolone 1-2mg/kg once daily is used with tapering according to clinical response. Courses are generally limited to 1-2 weeks.
- Longer term treatment is sometimes required for specific problems such as ABPA or persistent airway inflammation.

4.5.2 Inhaled Corticosteroids (ICS)

- Current evidence from randomised trials is insufficient to establish whether there is a beneficial or harmful effect of ICS when used in CF patients.[25]
- ICS prescription is widespread in CF, despite the lack of evidence.
  - ICS withdrawal is safe [26] and may minimise unnecessary drug burden.
- May be a role for ICS in CF patients with coexistent asthma (section 4.6).

4.5.3 Non-steroidal anti-inflammatory drugs (NSAIDs)

- Ibuprofen has been shown to produce a modest reduction in decline of FEV_1 compared to placebo in two separate trials over two and four years.[27]
- Modest benefit combined with the need to monitor blood levels and concerns over potential side effects (e.g. gastrointestinal haemorrhage) has meant that it is not used routinely in CF patients.
- In studies where ibuprofen has been used:
  - A high dose is used (typically 20-30mg/kg, with the dose titrated to achieve a peak plasma concentration of 50-100 microgram/mL), as low dose ibuprofen actually causes an increase in neutrophil number
  - Used a twice daily regimen, to maintain the neutrophil suppressive effect of the high dose.

This approach is not currently used at CHW and further research is required to outline its utility in CF.

4.5.4 Long acting beta-agonists (LABAs)

- Salmeterol reduces *P. aeruginosa* or *H. influenzae*-induced airway damage.[28, 29] Beneficial effects with combination ICS/LABA therapy are also reported.[30]
- Recent data suggests a potential beneficial role on mucociliary clearance.[31]

- LABAs may therefore have additional anti-inflammatory benefits when used for treatment of airway obstruction in patients with CF.
- LABA monotherapy is not recommended, and further research is required to outline the use of combination ICS/LABA therapy in CF.

4.5.5 Macrolide antibiotics

- Used for more than 20 years to treat chronic inflammatory airway diseases based on their immunomodulatory activity.
- First used in CF in 1991 in Japan. Several trials in CF to date with azithromycin.
- Initial studies used a daily dosage regime, although a three times weekly regimen appears comparable, (no direct comparison trial done to date).
- Documented benefits with treatment (Paediatric data):
    - Improvement seen in lung function at 6 months (6.2% in FEV_1, 5% in FVC vs. placebo) [32, 33] not maintained at 1 year [34]. The initial change in FEV_1 reported is similar to that reported with dornase alpha (Pulmozyme®).
    - Beneficial effect on exacerbations, time to first exacerbation, and number of antibiotic courses persists through to 12 months.[32, 34]
    - Benefits in *P. aeruginosa* and non-*P. aeruginosa* colonised subjects.
    - Benefits in nutritional outcomes at six months [32] not seen at one year [34].
- Side effects generally mild and self-limiting.
- Adult data suggests beneficial effects not maintained in 2nd year of treatment. [35]

Indications for commencing azithromycin:

No current international consensus regarding indications for commencement and dosing regimen.

Current indications at CHW to commence treatment are:

- FEV_1 <70% predicted.
- Chronic pseudomonas colonisation.
- Age 6 years or older.
- Clinical signs of chronic suppurative lung disease.
- Failure to improve or deteriorate on the above criteria despite aggressive and comprehensive respiratory treatment over the preceding 6 months.

Consider in chronic colonisation with *S. aureus* with FEV_1 <70% who have failed to improve or deteriorated over the preceding 6 months despite aggressive & comprehensive respiratory treatment.

- Response to treatment reassessed at 1 year and if there has not been improvement in parameters below, the medication should be discontinued.
    - Rate of decline in FEV_1.
    - Weight gain.
    - Improvement in the number of pulmonary exacerbations requiring hospital admission for IV antibiotics.
    - Number of oral courses of antibiotics in the past year.

- If azithromycin therapy is discontinued in the setting of initial beneficial impact that did not continue beyond one year, then consider re-starting after a period of treatment of 6-12 months, as clinically indicated.
    - On restarting azithromycin treatment, evaluation for beneficial impact is again required.
- Sputum should be screened for NTM due to the detrimental effects of azithromycin on *Mycobacterium abscessus* clearance.[36]:
    - Before starting treatment and at each visit whilst on treatment
    - If there is an unexplained decline
- During treatment, liver function tests should be monitored.
    - Increase > two times the normal value in either AST, ALT or GGT is an indication to discontinue treatment.
- Complete the "**Commencing Azithromycin in Patients with Cystic Fibrosis Form** [M49] and monitoring effectiveness of treatment:
  http://chw.schn.health.nsw.gov.au/o/forms/cystic_fibrosis/commencing_azithromycin_in_patients_with_cystic_fibrosis.pdf

4.6 Asthma and Cystic Fibrosis

- Considerable overlap between the symptoms of asthma and CF.
- Airway obstruction related to infection and airway inflammation may also respond to asthma treatment such as bronchodilators and systemic steroids.
- Indications for the consideration of regular asthma treatment include:
    - History of typical "asthmatic" symptoms, particularly if associated personal or family history of atopy.
    - Clinical response to bronchodilators.
    - Evidence of reversible airway obstruction on spirometry.
    - Atopic to inhaled allergens on skin prick testing.

4.6.1 Bronchodilator Therapy

- Use of a short acting beta-2-agonist bronchodilator (SABA, salbutamol) prior to physiotherapy should be considered if evidence of bronchodilator response on spirometry (defined as 12% increase in FEV_1 post bronchodilator).
- Symptomatic use of a SABA is appropriate for episodic wheezing (viral-induced, exercise-induced etc.).
- LABA (salmeterol, eformoterol) may be helpful for symptom control in children with persistent asthma not adequately controlled on low dose ICS.

  Note: LABA should not be used as monotherapy, and should only be used in combination with ICS.

4.6.2 Preventive Therapy

- Preventive non-steroidal/ICS therapy should be used to control frequent episodic or persistent asthmatic symptoms, according to the National Asthma Council Guidelines.
- There is no convincing evidence that these agents have a beneficial anti-inflammatory effect in CF immune-mediated lung disease.

4.6.3 Systemic steroids

- Oral prednisolone 1mg/kg daily for 5-10 days can be used for treatment of acute severe asthma complicating CF.
- More prolonged courses are often necessary in patients with CF, presumably because of their coexistent CF related airway disease.

4.7 Allergic Bronchopulmonary Aspergillosis (ABPA)

- Caused by complex hypersensitivity response to ubiquitous fungus: *Aspergillus spp*.
  - In CF, *A. fumigatus* is the most common species involved.
- Hypersensitivity activates TH_2 lymphocytes to promote an eosinophilic infiltrate.
- Fungal proteases activate airway epithelium to produce a chemokine response, and neutrophilic infiltrate with accompanying tissue damage and bronchiectasis.
- Results in an acute inflammatory reaction with symptoms of bronchospasm (mimicking asthma), and a subsequent secondary mixed infiltrate that can escalate and persist as chronic inflammation occurs.
- Host susceptibility factors may influence expression of the disease.
- Considerable overlap between pathology and clinical manifestations of ABPA and CF-related airway inflammation, which not only makes it difficult to document the actual prevalence of ABPA in patients with CF, but also the diagnosis itself.
- <u>*Overall prevalence*</u>:
  - 7.8% (range 2.1%-13.6%, European CF Registry data).[37]
  - Prevalence low <6 years of age. Almost constant at 10% after that age.
  - Equivalent Australian data (Australasian CF Data Registry 2009)
    - 7.7% of children <4 years and 25-30% of older children.
    - Increased rates compared to 2000 figures (0.7% and 4-6%, respectively).
    - Rates of Aspergillus sensitisation 4-5 times higher than ABPA
- Presence of ABPA associated with: [37]
  - Higher rates of microbial colonisation
  - Pneumothorax and massive haemoptysis
  - Higher IgG serum levels
  - Poorer nutritional status
  - Lower FEV_1.

4.7.1 Diagnosis

- Following criteria for diagnosis which have been recently proposed: [38]
- Diagnosis requires all immunological criteria and at least 3 of the supportive criteria.

Immunological criteria (**all below criteria are required for diagnosis**):

- IgE (skin prick test or RAST) positive to *A. fumigatus*
- IgG antibodies/precipitins to *A. fumigatus*
- Total IgE > 1000International Units/mL (American criteria)
- Reduction by >50% in IgE after 2 weeks of daily systemic corticosteroid therapy (**Note:** this is only apparent after therapy has been started)

Supportive criteria (**at least 3 are required for diagnosis**):

- Airway obstruction/wheezing.
- Pulmonary infiltration on CXR.
- Bronchiectasis on chest CT.
- *A. fumigatus* in sputum culture.
- Decrease in pulmonary function (>10% decrease FEV_1).

- On occasions ABPA diagnosis is made in CF patients who don't fulfil all the immunological and supportive criteria yet respond to treatment. [e.g. fulfil European criteria for IgE (>500International Units/mL) but not the American threshold above.]
- CHW patients are currently screened yearly for total IgE, with other tests such as *A. fumigatus* precipitins only done if ABPA is clinically suspected.

4.7.2 Stages to Disease

5 stages of disease and the progression is not necessarily sequential.

- **Stage 1** – initial acute presentation.
- **Stage 2** – disease in remission, with persistent immediate-type skin reactivity and precipitating antibodies to *A. fumigatis* antigens.
- **Stage 3** – exacerbation of symptoms, with all characteristics of stage 1.
- **Stage 4** – asthma in which control of symptoms is dependent on chronic use of high-dose corticosteroids.
- **Stage 5** – advanced fibrotic disease.

4.7.3 Treatment

- The current treatment protocol, at CHW is summarised on the next page.
- Systemic steroids remain the main stay of treatment for ABPA. Studies conducted, despite small numbers & varying corticosteroid regimens, suggest utility in the treatment of ABPA.[39, 40]
- Despite small studies suggesting benefit of ICS, larger studies have failed to provide evidence to support their use in the maintenance ABPA treatment.[41]
- Utility of pulse methylprednisolone, as an oral corticosteroid alternative, has been described.

Itraconazole

- Aspergillus colonisation may trigger increased airway inflammation and therefore, eradication may modify the course of the disease.
- Itraconazole has anti-allergic and anti-inflammatory properties because of its inhibitory action on 5-lipoxygenase.[42, 43]
- Use in asthmatics over 16 weeks demonstrated a reduction in inflammation associated with ABPA and improved clinical outcome, however none of the patients had CF.[44]
- Small case series in CF patients, have shown small improvements in lung function, symptoms or a reduction in oral corticosteroid use.[39, 45, 46]
- An important potential side effect of combined steroid and itraconazole use is adrenal suppression: 44% of patients receiving inhaled budesonide and itraconazole and [47] 83% of patients receiving inhaled fluticasone and itraconazole therapy.[48]

Aspergillus colonisation

- Data on the importance of Aspergillus colonisation is conflicting:
  - Independent risk for subsequent hospital admission.[49]
  - Increased incidence in those with increased inhaled antibiotic use but no associations with lower lung function or subsequent decline.[50]
- Subsequent intervention study investigating utility of itraconazole treatment in colonised subjects (without evidence of ABPA) failed to show benefit.[51]
- Lack of evidence to support treating colonised subjects at present.

Diagnosis of ABPA based on the clinical criteria outlined above or due to strong clinical suspicion of disease.

Start **Oral Prednisolone therapy at 2 mg/kg/day** (maximum 60mg/day)

- ❖ Continue at this dose for 2 weeks
- ❖ Wean to 1 mg/kg/day for 4 weeks (weeks 3-6)
- ❖ Wean to 0.5 mg/kg/ day for 2 weeks (weeks 7-8)
- ❖ Wean to 0.5 mg/kg/day on alternate days for 4 weeks (weeks 9-12).

- Clinical status may dictate a slower wean.
- If greater than three months received refer for:
  - ❖ DEXA scan
  - ❖ Oral glucose tolerance test.at the next interval check

Start **Oral Itraconazole therapy at 5mg/kg/dose** (max 200mg) **twice a day**

- ❖ Administration varies between oral solution and capsule forms (see below).
- ❖ Check serum trough levels monthly after starting. Adjust dose as necessary to achieve target therapeutic level of 500-1000 microgram/L and avoid toxicity.
- ❖ Monitor liver function tests
- ❖ Review therapy at 3 months (aim for minimum 6 month period of therapy)

Review monthly during oral corticosteroid treatment period

- Monitor the following at each review during treatment:
  - ❖ Clinical status, weight gain, and lung function
  - ❖ Blood tests during dual therapy: Serum trough itraconazole level, liver function tests, total IgE
  - ❖ Monitor: Urinalysis [glucose & ketones], BSL, and blood pressure whilst on oral corticosteroids.

Criteria to stop therapy:

- ❖ Return of lung function to baseline prior to diagnosis of ABPA
- ❖ Resolution of ABPA related clinical symptoms
- ❖ Decrease in IgE to below 1000 International Units

Consider the following in steroid dependent disease (stage 4 onwards) or in those with frequent ABPA exacerbations:

- Pulse methylprednisiolone therapy
  - ❖ 10 mg/kg/day intravenously for 3 consecutive days each month for 6 months
  - ❖ No daily oral corticosteroids prescribed between monthly pulses.
  - ❖ When adequate control is achieved increase interval between pulses as tolerated
  - ❖ Lower rate of side effects seen compared with daily oral corticosteroid therapy

In those who remain dependent on steroids beyond the 6 month treatment period of methylprednisolone, consider omalizumab as a steroid sparing agent

- ❖ Commenced following consultation with Immunology

Consider alternate antifungal agents if itraconazole therapy is not tolerated or if therapeutic levels of itraconzole are not achieved/maintained. Alternate antifungals should only be started after consultation with Infectious Diseases Team. Options include:

- ❖ Voriconazole
- ❖ Inhaled amphotericin

4.7.4 Additional notes regarding treatment

Itraconazole therapy

- Itraconazole should be given as either:
  - *Capsules* – taken with food and acidic beverage (e.g. Coca cola or orange juice)
  - *Oral solution* – taken on an empty stomach (i.e. 30 minutes before food or 2 hours after).
- If fail to achieve therapeutic serum trough levels (500-1000 microgram/L) then consider:
  - Stopping any proton pump inhibitors, H2 receptor antagonists and antacids if there is not a strong clinical indication to continue these therapies.
  - Trial of oral suspension, which although more expensive may achieve better trough levels. However, it may be poorly tolerated, particularly by older children who require large volumes.
  - Increasing dose to a maximum of 20mg/kg/day. This dose has been used in the literature and is also part of ABPA protocols at other CF units in Australia [RCH Brisbane].[52, 53]
- Reduce itraconazole dose if:
  - serum trough levels >1000 microgram/L; or
  - clinical signs toxicity occur - hepatotoxicity, nausea, vomiting, diarrhoea, headaches and tingling of hands and feet have been reported.
- Important interactions:
  - Rifampicin (CYP450 3A4 inducer) - consider alternative anti-staphylococcal therapy.
  - There are reports in the literature of enhanced risk of adrenal suppression when using concomitant ICS with itraconazole - review the need for ICS therapy.[48]
- Failure to achieve adequate therapeutic levels during therapy may be contributing the high rates of azole resistance reported in adult CF subjects.[54]

Voriconazole therapy

- Voriconazole may be better tolerated, but should only be started after careful consideration and discussion with Infectious Diseases due to the reported side effects with long term therapy:
  - Include photosensitivity and squamous cell carcinoma.[55, 56]
  - Photosensitivity risk does not appear to be related to the serum levels of voriconazole achieved.
- Sustained efforts to optimise itraconazole levels are the preferred approach to anti-fungal management, unless escalation in severity of clinical disease dictates otherwise.

Omalizumab therapy

- Omalizumab is an anti-IgE monoclonal antibody which has been shown to be effective at reducing or eliminating the need for steroids.
- Omalizumab dosing in other conditions is based on IgE serum levels and weight. However this is not appropriate in ABPA since IgE levels are significantly in excess of the dosing algorithm.

- Referral to Immunology to decide on suitability and if suitable, the dose, frequency and duration of treatment.

4.7.5 Physiotherapy management in ABPA

- Optimising airway clearance is important in patients with ABPA.
- Usual airway clearance routines may have to be modified based on response and symptoms.
- Hypertonic saline can be continued in many patients with monitoring [2] however ensuring adequate bronchodilator pre-treatment or reducing strength of hypertonic is often required.
- If patients are requiring high dose steroids, be aware that bone mineral density may be affected; therefore encourage weight-bearing/high impact exercise.

4.8 Mucolytics and Osmotic agents

Over the last two decades, much clinical research has concentrated on breaking down the components of the mucus in order to facilitate expectoration of sputum.

4.8.1 Dornase Alpha (Pulmozyme®)

- The two macromolecules that contribute to the physical properties of secretions are mucus glycoproteins and DNA.[57]
- Chronic bacterial infection in the airways leads to accumulation of leukocytes.
- Leukocytes liberate extracellular DNA, which contributes approximately 10% of the dry weight of respiratory secretions [sputum] from patients with CF.[58]
- Solutions containing high concentrations of purified high molecular weight DNA are highly viscous, thereby harder to expectorate.[57]
- Deoxyribonuclease is a human enzyme in saliva and blood that digests extracellular DNA.
- Recombinant human DNase (dornase alpha, or Pulmozyme™) was developed as an inhaled mucolytic agent to reduce sputum viscosity, to aid expectoration.
- Enhanced mucociliary clearance reduces bronchial obstruction, bacterial proliferation and the rate of progression of bronchiectasis.
- A number of studies have shown utility in CF.
    - Largest single trial (n=643) showed good tolerability and resulted in a mean improvement in FEV1 of 5.8% and lowered exacerbation rate by 28%. No difference between once and twice daily treatment was seen.[6]
- Used once daily. Equally effective either 30 minutes before or after physiotherapy/PEP mask therapy [59] according to patient preference.

Failure to use medication regularly results in benefit wearing off within 2 weeks.

Eligibility Criteria for Dornase Alpha (Pulmozyme)

Age 5 years and over

- Evidence of suppurative lung disease
- Chronic respiratory symptoms (including chronic or recurrent cough, wheeze or tachypnoea) requiring frequent hospital admissions more frequently than 3 times per year
- Clinical stability
- Repeatable and reproducible spirometry (minimum age 5 years)
- FVC > 40% predicted

Age < 5 years

- Severe clinical course with frequent respiratory exacerbations, **or**
- Chronic respiratory symptoms (including chronic or recurrent cough, wheeze or tachypnoea) requiring frequent hospital admissions more frequently than 3 times per year; **or**
- Significant bronchiectasis on chest high resolution computed tomography scan; **or**
- Severe CF bronchiolitis with persistent wheeze non-responsive to conventional medicines; **or**
- Severe physiological deficit measure by forced oscillation technique or multiple breath nitrogen washout and failure to respond to conventional therapy.

- Government-subsidised use for children 5 years and older is limited to patients who demonstrate maintenance of lung function at the end of a 3 month trial.
- Trials can be repeated after a four week wash out period if unsuccessful.
- Children less than 5 years must be reassessed at 6 monthly intervals.
- Dornase alpha (Pulmozyme) is dispensed through the CHW pharmacy. Dornase alpha (Pulmozyme) should be prescribed on a separate prescription which is endorsed with a valid prescriber number and the appropriate PBS S100 streamlined authority number. See the PBS website for current authority numbers & details: http://www.pbs.gov.au/medicine/item/5704F-6120D

4.8.2 Hypertonic saline (HTS)

- Prolonged effect on increasing the amount of airway surface liquid in epithelial cells in vitro [60] contrary to the previous belief that it was a short lived effect.
- Daily HTS use over a 48 week period led to a reduction in pulmonary exacerbation number, compared to placebo.[61]
  - FEV_1 was marginally improved in the HTS group.
  - Treatment compliance was 64%.
- Exact underlying mechanism of benefit remains unclear, whether it is due to an increase in the volume of airway surface liquid, an increase in airway clearance through induction of cough, or both.
- Beneficial effects on *P. aeruginosa* motility have been reported.[62]

Indications for commencing a trial of hypertonic saline include:

- Age <5 years and clinically symptomatic suppurative lung disease
- Aged ≥5 years **and**
  - ❖ no significant improvement with Pulmozyme
  - ❖ significant symptoms of suppurative lung disease and used as adjunct to Pulmozyme

- Bronchoconstriction is an important and common side effect:
  - Tolerance test conducted prior to starting to ensure tolerance.
  - A bronchodilator may be required prior to administration in patients with documented bronchoconstriction.
- Exact role and optimal concentration of HTS in the management of CF has yet to be determined.
  - A variety of different strengths of hypertonic saline are used in the literature; at present our pharmacy stocks a 6% concentration.
  - Hypertonic saline should be trialled at 6% for most patients, except for those less than 2 years. For infants or if 6% HTS is not tolerated, a trail of 3% should be given.

4.8.3 Inhaled Dry Powder Mannitol

- Non-ionic sugar based hyperosmolar agent.
- Shown to increase sputum clearance in adult patients with CF [63] equivalent to 6% HTS when directly compared.
  - As opposed to nebulised HTS, mannitol is inhaled as a dry powder.
- Benefits demonstrated in outpatient and inpatient setting:
  - Use over a one year period (400mg twice daily) led to improvements in FEV_1 (8% above baseline).[64]
  - A pilot study conducted at CHW as an adjunct to normal therapy during hospital admissions for treatment of acute pulmonary exacerbation suggested benefits in lung function response seen, compared to placebo.[65]
- Further research is needed to determine its exact role in CF management.
- At present within the CHW CF clinic, it is trialled in those subjects felt to benefit from additional secretion clearance, who:
  - have either failed previous trials of HTS or Pulmozyme therapy or
  - are already on these medications but whose clearance could be optimised.
- As with HTS, bronchoconstriction is a common side effect.
- A test dose is required before mannitol can be prescribed on an ongoing basis. If FEV_1 falls by 20% or more during the trial, the patient is not eligible for mannitol therapy. Pre-treatment with salbutamol is recommended for both test and maintenance doses.
- Mannitol is dispensed through the CHW pharmacy. Mannitol (Bronchitol) should be prescribed on a separate prescription which is endorsed with a valid prescriber number

and the appropriate PBS S100 streamlined authority number. See the PBS website for current authority numbers & details: http://www.pbs.gov.au/medicine/item/2008Q-2015C

Indications for commencing a trial of Mannitol:

- Aged six years and above
- Evidence of suppurative lung disease
- FEV_1 greater than 30% predicted.
- As either an add-on therapy to dornase alpha or in patients intolerant to, or inadequately responsive to dornase alpha.

4.9 Oxygen Therapy & Non-Invasive Ventilation

- Progressive deterioration of lung function in CF patients may lead to significant hypoxaemia and hypercapnia, especially during sleep.
- Patients with moderate to severe pulmonary disease (FEV_1 < 50%) are at risk for hypoxaemia.
- However, patients in whom there has been a rapid decline in pulmonary function, especially teenage girls, may unexpectedly deteriorate to the point of needing oxygen or non-invasive ventilation (NIV) within 12 months of their previous assessment.
- Initially, hypoxaemia resulting from ventilation-perfusion mismatch occurs in the presence of tachypnoea and increased respiratory effort. This is most likely to occur during sleep, exercise and with intercurrent exacerbations of suppurative lung disease.
- Subsequently, as lung disease progresses and the patient's ability to exercise wanes, CO_2 retention develops as respiratory failure develops.
- The presence of CO_2 retention should be suspected in patients reporting disrupted sleep with morning headaches.
    - An elevated arterial CO_2 or venous serum bicarbonate is suggestive of the need for further investigation of the degree of respiratory failure.
    - This may be readily assessed using overnight polysomnography.

Polysomnography (PSG)

- Involves an overnight outpatient admission to the Sleep Unit (Turner Ward) for the patient and one parent if desired.
- Sleep stage, pattern of breathing, work of breathing and levels of O_2 saturations and transcutaneous CO_2 are measured continuously.
- This often involves a study in room air followed on a subsequent night in oxygen, nasal continuous positive airways pressure (nCPAP) or bi-level pressure support (BiPAP) with or without supplemental oxygen. In more advanced lung disease correcting hypoxaemia with nasal catheter oxygen may lead to a parallel rise in CO_2.[66]
    - In this setting, non-invasive ventilation (CPAP or BiPAP) in all but end-stage lung disease should overcome the CO_2 retention.[67]

- Organised in consultation with one of the hospital's sleep physicians contacted via Respiratory Medicine, generally when the patients are clinically stable.
- Indications for PSG
  - FEV_1 < 50% predicted.
  - Work up for lung transplantation.
  - Other established indications for PSG – e.g. chronic snoring of history suggestive of sleep disordered breathing.

Supplemental oxygen

- Seen as a fore-runner of the need for NIV.
- NIV would be necessary in a minority of patients in the adolescent age group, whilst supplemental oxygen may be needed in approximately 20-30% by the time of transfer to an adult service.
- Currently, no published data to guide prescription of long term oxygen supplementation for CF patients with advanced lung disease.[68]
- Supplemental oxygen may also be required during air travel. Reduced air pressure on board of an airplane can cause a drop in oxygen saturations during a flight.
  - A fitness to fly test (Hypoxic challenge test) is indicated in:[69]
    - Any CF patient intending to fly with a baseline FEV_1 <50% predicted.
    - If oxygen saturations fall to less than 90% during the assessment then supplemental oxygen during flight is indicated.

4.10 Haemoptysis

- The exact pathogenesis of haemoptysis remains unclear.
  - Persistent airway inflammation and vascular growth may result in markedly enlarged and tortuous bronchial arteries [70] at systemic pressure that sit close to the bronchi.
  - Chronic and acute inflammation weakens the vessel wall.
  - Subsequent bleeding into the bronchial lumen.
- 60% of CF sufferers > 18 years will have had haemoptyses, mostly minor ones. In a recent decade review of the US CF registry: [71]
  - 4% incidence of massive haemoptysis (only 25% < 18 years of age).
  - 26% had recurrent episodes.
  - Clear association with increasing age, and severe lung disease (60% had FEV_1 <40% predicted).

4.10.1 Assessment

Minor Haemoptysis

- Blood streaking in sputum or small amounts of fresh blood, usually part of respiratory exacerbation.

Major Haemoptysis, either of

- Large volume, greater than 200mL/day.
- Recurrent bleeding, greater than 100mL/day, occurring over several days.
- May be life threatening, by causing either obstruction of the airway (asphyxiation) or hypotension, and may require transfusion.

4.10.2 Management

Unless the airway is compromised, always follow a conservative approach.

- Arrange chest X-ray.
- Exclude underlying cause, e.g. clotting defects, platelet reduction.
- Be sure it is haemoptysis, not haematemesis.
- Commence IV antibiotics, "tune-up".
- Stop any NSAID medications (due to effect on platelet function)
- Reduced physiotherapy until acute fresh bleeding settles as shown below.

For Blood-streaked sputum:

- Normal exercise routine
- Reduce the force of coughing – teach controlled huff and cough

For Minor Haemoptysis (<200mL/24hrs)

- *Cease:*
  - Percussion / vibrations and oscillatory PEP techniques
  - Hypertonic saline
  - Vigorous exercise
- *Continue:*
  - Dornase alpha (Pulmozyme)
  - PEP therapy with controlled, gentle huff and coughs
  - Ensure adequate humidification to ease sputum expectoration
  - Encourage walking

For Major Haemoptysis (>200mL/24hrs)

- If active bleeding, put into high side lying position with bleeding side facing down
- Cease airway clearance and exercise until active bleeding resolved, then continue as per minor haemoptysis
- Bed rest

If recurrent, consider:

- Angiogram and embolization of large bleeding vessels.
- Other treatment options include atenolol [72] and tranexamic acid [73] although the only available evidence for these treatments is based on small case series or individual case reports.

4.11 Pneumothorax

- More common with increasing age and severity.
- Effects depend on the pre-existing lung state and the size of leak.
- Symptoms vary from asymptomatic to shoulder tip pain with sudden deterioration.
- Size estimate based on current British Thoracic Society guidelines, 2003.[74]
    - Small: Rim of air <2cm at the level of the hilum or <3cm at the apex
    - Large: ≥ 2cm at the level of the hilum or ≥3cm at the apex.

4.11.1 Management

Small / asymptomatic:

- Observe only.

Symptomatic / large:

- Intercostal chest catheter (ICC) insertion
    - Insertion ideally by interventional radiology or surgeon, or if more urgent, on the ward by a doctor experienced in the procedure
    - Small bore pigtail catheter should be used
- Suction should be applied at 1-3kPa.
- Consider change to larger bore chest tube if fails to resolve with above measures after 48-72 hours

Recurrent/persistent leak:

- 30–50% of pneumothoraces will recur/persist.
- Ensure adequate analgesia to allow effective cough, physiotherapy and mobilisation when ICC is in place. This may require opiates or administration of local anaesthetic via a pleural catheter.
- Consider bronchopleural fistula.
- Refer to surgeons.
- Further management may include:
    - Repeat tube thoracostomy (depending on physical state) *or*
    - Limited thoracotomy, with apical resection of blebs, mechanical abrasion (pleurodesis), or chemical pleurodesis.
- It is important to remember the following in children with pneumothorax, secondary to pre-existing lung disease, compared to primary pneumothorax.[75]
    - Shortness of breath is usually more severe, and hypercapnia may be present.
    - Symptoms do not resolve spontaneously.
    - Examination findings may be more subtle as they can be masked by underlying disease.
- For further information see the CHW Spontaneous Pneumothorax Management Practice Guideline.

4.12 Chapter 4 References

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5 Gastrointestinal Management

5.1 Pancreatic Disease

5.1.1 Pancreatic Insufficiency

- By mid to late childhood only 10% to 20% of the total population of CF patients remain pancreatic sufficient (PS).[1, 2]
    - Includes a variable proportion of initially PS patients during infancy who suffer a subsequent deterioration of their pancreatic function.
- Occurrence of pancreatic insufficiency (PI) or PS appears to be linked to genotype.
    - Almost all pF508.del homozygotes and 70% of heterozygotes were PI in one study.[3]
- Those who have changed from PS to PI are usually pF508.del homozygotes, while those who remain PS have at least one mild mutation, e.g. R117H, A455E, R347P, 3849+10kbC~T.
- Patients who become PI may have obvious symptoms (e.g. failure to gain weight or weight loss, oily stools etc) but some remain asymptomatic.
- Formal 3-5 day fat balance study estimating faecal fat as a percentage of fat intake should be performed:
    - At diagnosis
    - In PS patients prior to school entry
    - In those who develop symptoms of malabsorption
- Faecal fat excretion >7% of fat intake indicates malabsorption and the PI phenotype.
- PI patients should receive oral pancreatic enzyme replacement therapy (PERT) using one of the microspheric preparations at a dose of 5,000International Units lipase/kg/day with a maximum dose of 150,000International Units/day (equivalent to 15 standard 10,000International Units capsules/day).
    - Studies in adolescents (>30 kg) have shown average fat excretions of 11% to 15% of fat intake on the latter dose with little if any improvement on higher doses.[4, 5]
    - Higher dose lipase preparations are available (up to 25,000International Units lipase/ capsule) and may be appropriate for older patients

Recommended PERT dose: 5,000-10,000 International Units/kg/day

- Patients taking high dose preps should be monitored carefully to ensure their PERT dose does not creep above the recommended.
- Excessive doses of PERT (>10,000International Units/kg/day) have been associated with the development of Fibrosing Colonopathy (FC).[6]
    - FC is a non-inflammatory, colonic obstruction associated with marked intramural fibrosis, usually in the ascending or transverse colon[7] and associated with considerable morbidity.

5.1.2 Pancreatitis

- Up to 10% of PS patients will develop pancreatitis.
- Generally felt not to occur in PI patients who have lost their functioning acinar activity, but has been reported in PI subjects:
  - Incidence of 0.5% of PI patients in one large European wide study.[8]
  - Remains a contentious issue, due to concerns over the accuracy of pancreatic function assessment in these patients.
- Management is similar to non-CF pancreatitis:
  - IV fluids
  - nil by mouth
  - analgesia
  - If the pancreatitis returns an ultrasound and MRCP should be performed.
- "Biochemical pancreatitis":
  - Represents incidentally diagnosed raised lipase and amylase without evidence of clinical symptoms.
  - Should be managed conservatively.
  - Previous studies have shown that levels of amylase and lipase fluctuate in and out of their normal ranges in PS patients followed longitudinally.

5.2 Liver Disease

5.2.1 Incidence and Diagnosis

- Up to 40% of patients develop **Focal Biliary Cirrhosis (FBC)**: Consists of focal scarring of the liver and is pathognomonic of CF.
- Up to 10% develop **multilobular biliary cirrhosis (MBC)**: Associated with portal hypertension and/or liver failure.
- Presence of liver disease has not correlated with the severity of lung or intestinal disease:
  - It has been described in three patients with PS and no detectable abnormalities in pulmonary function.[9]
  - It is not clear why some patients develop liver disease and others do not, however modifier gene effect on CFTR function is a possible aetiology.
- Diagnosis of FBC is difficult.[10]
  - *Clinical examination:* patients may have enlarged livers which are firm to palpation and some will have abnormal liver function tests. However the clinical exam is subjective and many with normal LFTs have FBC.
  - *Abdominal ultrasound:* may demonstrate increased echogenicity of the liver not related to fibrosis but attributable to impacted secretions or the presence of parenchymal steatosis.

- *Liver biopsy:* has poor sensitivity for diagnosing FBC because of the sampling error.
- *MRI scanning:* can recognise focal scarring but its specificity and sensitivity have not been evaluated.

- In contrast, MBC can be recognised by:
  - *Clinical examination:* enlarged lobulated liver with or without splenomegaly.
  - *MRI scanning:* confirmatory.
  - *MRI angiography*: can also define the presence of portal hypertension.
- Ultimately, a combination of findings (clinical, imaging, and biochemical) is used to determine the onset and progression of this complication.

5.2.2 Medical management of liver disease

Ursodeoxycholic acid:

- Hydrophilic bile acid, theoretical possibility of enhancing fluid secretion from the biliary tree.
- Whilst initial studies were promising[11, 12] a recent Cochrane Collaboration report has questioned the validity of its routine use in CF.[13]

Biliary scintigraphy and MRCP:

- Our unit has found that common bile duct stenosis is a frequent occurrence in patients with liver disease and that biliary diversion surgery appears to prevent the progression of FBC to MBC.
- Patients presenting with evidence of liver disease should have biliary scintigraphy and an MRCP to determine if the patient has a common duct stenosis which may be amenable to surgical intervention.

If portal hypertension is present:

- Less than 50% will develop oesophageal variceal bleeding. As such, prophylactic therapy has not been recommended.
  - Some units use propranolol but currently there are no CF studies supporting its use.
- If variceal bleeding occurs:
  - Banding or sclerotherapy can be used to obtain haemostasis.
  - If bleeding is not controlled by the above, portal-systemic shunt surgery should be considered using a reversed lieno-renal shunt.[14]
  - Coagulopathy must be corrected and appropriate amounts of blood products must be available for transfusion.

A small number of patients with MBC will develop synthetic liver failure, with a decreased serum albumin and/or a coagulopathy.

- Consider for liver transplant if FEV_1 >50% predicted and no fungal colonisation or intercurrent infection with *B. cepacia*.
- Post-transplant survival at least consistent with non-CF liver transplant patients, with 70-80% 5 year survival.[15]

5.3 Abdominal Pain

5.3.1 Acute Abdominal Pain in CF

- This is common and has many causes.
- Can be acute, mimicking surgical emergencies.
- Concurrent antibiotics and other therapies may mask physical signs
- Surgery should not be undertaken without exhaustive consideration of possible causes.

Consider:

- Distal intestinal obstruction syndrome (or meconium ileus equivalent) - inspissation of intestinal contents in the terminal ileum and caecum.
- Gall stones - suspect biliary causes in patients with pain in the Right Upper Quadrant.
- Common bile duct stenosis.
- Oesophagitis.
- Peptic ulcer disease.
- Terminal ileitis.
- Pancreatitis (usually pancreatic sufficient patients).
- Renal stones.
- Don't overlook the possibility of a typical surgical emergency, e.g. appendicitis or intussusception.

Appendiceal disease

- Suspect in patients with pain in the Right Lower Quadrant (RLQ).
- Usually if appendiceal inflammation is present the patient will demonstrate rebound tenderness in the RLQ.
- Appendicitis is less common than in the non-CF community (1 versus 7%, respectively), but diagnostic delays are of considerable concern in CF, with a high risk of perforation or abscess formation.[16]
- Be prepared to re-evaluate these patients frequently.

DIOS

- Most DIOS cases will have a large usually non-tender mobile mass in the RLQ with or without x-ray evidence of intestinal obstruction.
- DIOS should be differentiated from CF related constipation

CF related constipation, defined as:

- Abdominal pain and/or distension
- Reduced frequency of bowel movements or increased consistency of stools in last few weeks/months

Above symptoms are relieved by the use of laxatives. Enemas may be required depending on the initial response to oral laxative medications.

Consider the following Investigations in any child presenting with abdominal pain:

- *Blood tests:* including full blood count, electrolytes, liver function tests, CRP, amylase, lipase
- *Abdominal X-ray:* erect and supine/decubitus.
- *Abdominal Ultrasound scan:* to ensure that any palpable mass is not an intussusception or an appendix abscess or infected "mucocoele" of the appendix.
- *DISIDA scan:* consider if possible biliary tract disease.
- *Abdominal CT:* may be needed if any doubt about possibility of appendiceal disease.

Early surgical referral should be made as appropriate.

5.4 Distal Intestinal Obstruction Syndrome (DIOS)

5.4.1 Severity Grading of DIOS

DIOS can be graded as either incomplete or complete as outlined by the criteria below, and should be differentiated from CF related constipation: [17]

	Incomplete DIOS	Complete DIOS
Faecal mass in the ileo-caecum	Yes	Yes
Abdominal pain and/or distension	Yes	Yes
Complete intestinal obstruction as evidenced by bilious vomiting and/or fluid levels in small intestine on abdominal X-ray	No	Yes

5.4.2 Risk factors and Prevention

Risk factors for DIOS:

- Severe genotypes (present in almost 80% of cases, of which 2/3 were dF508)
- Pancreatic insufficiency (<10% of cases are pancreatic sufficient)
- Previous history of meconium ileus at birth
- Previous DIOS episodes(s)
- Fat malabsorption (inhibition of gastric emptying and prolonged intestinal transit times)
- Dehydration
- Transplantation

Prevention:

- Maintaining adequate hydration
- Adequate salt intake
- Adequate Creon dosage and compliance
- Laxative therapy
- Increased fibre intake (although not strong supportive evidence).

5.4.3 Management of DIOS

- The management protocol for DIOS is summarised below.
- Management may be individualised based on previous experience in recurrent DIOS.

Management of DIOS

All children presenting with DIOS should have the following:

- *Joint admission through ED*: Respiratory (AMO1) and Gastroenterology (AMO2)
- *IV access:* Full maintenance IV fluids plus dehydration correction.
- *Blood tests:* Full blood count, electrolytes, liver function tests, CRP. Additional blood tests as indicated based on differential diagnoses considered.
- *Abdominal X-ray*
- *Abdominal ultrasound scan:* to ensure that any palpable mass is not an intussusception or an appendix abscess or infected "mucocoele" of the appendix.

Incomplete DIOS without Small Intestine obstruction

- *Oral laxatives:* Lactulose (1mL/kg bd) or high dose liquid paraffin. Be aware there are emulsified and non-emulsified preparations with differing doses
- If no response over 48 hours or if pain intensifies consider anterograde flush out (e.g. ColonLYTELY or Glycoprep) administered via NG tube:
  - ❖ Volume and rate often based on child's ability to tolerate.
  - ❖ Gastrografin is not used due to risk of aspiration induced lung damage.
  - ❖ Discontinue oral laxatives during this stage of management.
- Acetylcysteine has been used orally for DIOS (Rectal enemas have less favourable results than oral)
- Repeat anterograde flush out if no response after 12-24 hours
- If no response after 12-24 hours of repeat anterograde flush out consider retrograde (i.e. PR) flush out. ColonLYTELY or Glycoprep may be used, via rectal tube (set up and performed by Gastroenterology fellow).

❖ Microlax or phosphate enemas are not felt to be useful for dislodging right iliac fossa (RIF) masses as this will only soften stool in the rectum.

Complete DIOS with evidence of small intestine obstruction

- Surgical consult
- IV fluid resuscitation
- Nil by mouth and NGT insertion (on suction)
- Retrograde flush out

❖ Consider gastrografin or N-acetylcysteine based enema (under radiological guidance) based on surgical opinion

❖Anterograde flush out is unlikely to be tolerated in this situation.
Acetylcysteine has been administered rectally. Varying doses, concentrations and volumes have been used.

Other aspects of management for all patients:

- All patients admitted with DIOS should be reviewed by the CF dietitian to assess Creon use, salt intake and other potential precipitating factors.
- *If* possible, agents which slow gut motility should be avoided.

5.5 Gastroesophageal reflux (GOR)

- Reported in up to 25% of CF patients[18] and at least 50% of those with GOR will develop oesophagitis.[19]
- Reflux is probably a multifactorial problem contributed to by: [20]
    - Severity and treatment of lung disease
    - Drugs that relax the lower oesophageal sphincter
    - Physiotherapy.
    - Delayed gastric emptying may continue, but the most significant feature to date is intermittent and inappropriate lower oesophageal sphincter relaxation.
- Patients with GOR may complain of:
    - Heartburn
    - Waterbrash
    - Dysphagia
    - Regurgitation.
    - Anorexia – may be the sole symptom. Therefore, patients experiencing weight loss or poor weight gain may have oesophageal disease.
- Investigations to consider should include:
    - pH study
    - Barium contrast examination: looking for strictures or a hiatal hernia.
    - oesophagogastroscopy of the oesophagus and stomach: looking for oesophagitis
- Management:
    - If oesophagitis present, treat with either H2 receptor antagonists or proton pump inhibitors.
    - Medical treatment should be prolonged for at least 6 months
    - Consider surgery for those unresponsive to medical therapy.[1]

5.6 Miscellaneous Small Intestinal diseases

5.6.1 Giardia infection

- Reported in 28% of CF children.[21]
- Important differential in patients with chronic diarrhoea
- Often misinterpreted as a failure to respond to PERT.

5.6.2 Crohn's disease

- Should be suspected in cases presenting with abdominal pain, anaemia, hypoproteinaemia, and extra-gastrointestinal manifestations (e.g. arthritis).
- Barium contrast imaging may demonstrate the typical segmental cobblestoned appearance, and histological examination will establish the presence of granulomatous colitis or ileitis.
- Treatment should be as for non-CF patients.

5.6.3 Coeliac disease

- Should be considered in those with ongoing symptoms of malabsorption despite compliance with optimal doses of PERT.
- Need for small bowel biopsy should be governed by positive serum antibody screening.
    - Anti-endomyseal antibodies or antibodies to tissue transglutaminase.
- Cases with a positive diagnosis should be managed with a gluten-free diet.

5.6.4 Rectal prolapse

- Occurs in 10-20% of CF patients, usually prior to 5 years of age.[22]
- May be the presenting feature of CF.
- Far more common in PI patients:
    - Occurrence has been attributed to large bulky stools in wasted patients prior to diagnosis or to ongoing malabsorption in patients following diagnosis.
    - It has been described in PS patients.[2]
- *Investigations*:
    - All children presenting with isolated rectal prolapse should have a sweat test.
- *Management*:
    - In most cases, rectal prolapse is a self-resolving problem and requires no specific therapy other than
        - Ensuring compliance with PERT
        - Providing laxatives if the patient is constipated.
    - Pararectal triple saline injection therapy under anaesthetic may be indicated for persistent or recurrent cases.[1]

5.7 Chapter 5 References

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6 Nutritional Management

The recommendations in this chapter are based on local experience as well as national[1] and international guidelines. [2, 3]

6.1 Background

- Nutrition is well recognized to play an important role in CF management.[1-3]
  - Nutritional status is an independent risk factor for survival in CF subjects
- Growth, as determined by BMI is an independent risk factor for survival in the paediatric population.[2]
  - BMI of >50th centile is associated with a lower risk of morbidity and mortality
  - Correlation exists between BMI centile and lung function in patients with CF
- Nutrition also plays an important role in the prevention and/or management of a number of CF complications including CFRD, bone health, CFLD, DIOS, malabsorption and GORD.[1-3]
- CF dietary recommendations differ from the dietary guidelines for the general population.[1-3] The main differences are that the CF diet should be high in:
  - **Energy** - 120-150% of the RDI for energy compared to the healthy population
  - **Fat** – children > 5years require 100g fat daily to help meet energy requirements
  - **Salt** – requirements start at approx. 1/4 tsp during infancy and increase with age
- Children with CF have elevated energy requirements due to:[3]
  - Increased energy expenditure which occurs as a result of lung infections and increased work of breathing.
  - Malabsorption: Approximately 80% of children with CF are pancreatic insufficient (PI) and require pancreatic enzyme replacement therapy (PERT) with foods containing fat to prevent malabsorption.
  - Inadequate oral intake as a result of poor appetite, commonly due to infection and inflammation.

6.2 Role of the Dietitian in CF

To work within the multidisciplinary team to:[1]

- Undertake nutritional assessments for all CF patients annually, or more frequently as clinically indicated. (Table 6.1)
- Ensure communication of nutrition issues within CF multi-disciplinary team
- Conduct ongoing nutritional surveillance
- Complete quality improvement and research projects within the area of CF
- Advocate for optimal nutrition in all paediatric CF patients

6.3 Aims of Nutritional Management[1]

1. Optimise growth:
    i. 0-2 years: % Ideal body weight (IBW) of 90% or greater.
    ii. 2-18 years: BMI > 50th centile and achieve estimated genetic height potential based on mid-parental height (MPH).
1. Optimise nutritional adequacy of the diet: Including macro and micronutrient intake.
2. Optimise PERT.
3. Optimise salt intake & hydration statues.
4. Optimise dietary recommendations where comorbidities exist such as CF related diabetes (CFRD), CF liver disease (CFLD), DIOS, gastro-oesophageal reflux (GOR) and bone density.

6.4 Nutrition Screening & Review Processes

- All CF patients are routinely screened by the nutrition assistant prior to their clinic appointment and on admission to clinic using the following tool (Table 6.1)

Table 6.1: CF Nutrition Screening Tool

Category	1) BMI percentile	2) Weight loss OR Weight Plateau*	3) Within Genetic Height Potential#	Urgency Dietetic Intervention
Overweight	BMI >97 %	→	→	Additional screening with nutrition assistant at clinic Review with dietitian as required when able, when requested and at Interval Check
Optimal	50-96 %	NO	YES	
Acceptable	50-96 %	NO	NO	Screen growth at clinic **Review this clinic if height z-score or BMI decreasing** Additional screening with nutrition assistant at clinic
	25-49 %	NO	→	
High Risk	25-96 %	YES	→	**Dietitian review this clinic**
	10-24 %	→	→	
Nutritional Failure	**<10 %**	→	→	

6.4.1 Outpatient Services

- All CF outpatients are to be seen by either a CF Dietitian or Nutrition Assistant at each outpatient clinic.
    - A nutrition assistant can only give information related to food variety, options and ideas i.e. lunchbox snack options and high calorie recipe ideas.

A Dietitian must be referred to for specific individualised recommendations, enzyme or salt dosing and modifications in principles of dietary education.

Indications for CF Dietitian review:

- **Priority 1**
  - Annual reviews
  - All patients screened as high risk or nutritional failure category
  - Patients <2yrs of age
  - Patients with a gastrostomy or CFRD
  - CF physician referrals
- **Priority 2**
  - Patients screened as acceptable, optimal or overweight category
  - Parents requesting to speak with a Dietitian
  - Nutrition assistant identifies need for review

Indications for Nutrition Assistant review:

- Review all patients not seen by the CF Dietitian.
- Completes screening tool to identify additional nutritional concerns (Table 6.1)

6.4.2 Inpatient Services

Role of Nutrition Assistant

- To see all CF inpatients within 24-48hrs of admission and is responsible for:
  - Ensuring each patient is on a CF diet code
  - CFRD patients are to remain on the CF diet code (not diabetes code)
  - Issue each patient with CF extras list & ordering specific meal/snack preferences
  - Ordering gastrostomy feeds for CF patients (based on home regimen)

Role of CF Dietitian

- To perform a nutrition assessment for all inpatients during 1st week of admission:
  - Minimum twice weekly reviews (with recent weights) required
  - Communication of progress at multidisciplinary CF ward rounds and meeting

6.5 Nutrition Assessment: Infancy – Adolescence[1]

A detailed nutrition assessment should be conducted at a minimum of once yearly (at the annual review).

6.5.1 Growth

- Individual weight and height measurements are entered into PowerChart at every outpatient clinic visit and the beginning/end of each admission.
- Weight, height & BMI centiles (>2years) & z-scores are monitored on computer generated CDC growth charts.
- Assessment:
  - Interpretation of Growth trends

Note in CF, poor height growth may be as a result of stunting from long term insufficient adherence to nutritional recommendations or prolonged steroid use.

- Significant weight gain or loss and any significant changes in BMI centiles.
- Mid-parental height (MPH) using reference equations that are built into PowerChart.
- Provide an individualised goal weight.

6.5.2 Biochemistry

- Routine bloods performed at the time of annual review: EUCs, LFTs and fat soluble vitamins (A, D and E)
- Additional bloods for nutritional markers on request may include: Iron studies (serum iron, transferrin, ferritin), zinc, vitamin B12 & magnesium.
- Inflammation can result in a false elevation or reduction in some markers & CRP should always be considered when interpreting biochemistry results.

6.5.3 Specific Nutrition Requirements

- Energy: 1.2-1.5 times the energy intake of a healthy individual without CF
- Protein: Recommended dietary intake (RDI) for age and 15% total energy intake
- Fluid: Minimum of 1-1.5L for children and 1.5-2L for adolescents
- Salt: ¼ - 3 teaspoons daily (as per Table 6.2)
  - Particularly important in infancy, in the warmer months and while exercising
  - Clinical signs/symptoms of poor hydration and salt intake include;
    - Hyponatraemia
    - Nausea/vomiting
    - Muscle cramps
    - Build-up of sodium chloride crystals on the skin
    - Fatigue
    - Poor concentration
    - Headaches
    - Thick secretions
    - Constipation or DIOS

Table 6.2. Recommended sodium intake for CF infants, children & adolescents [1]

	Sodium (mg)	Salt (teaspoons)
Infants	500-1000	¼ - ½
Children	1000-4000	½ - 2
Adolescents	6000	3

Table 6.3. Sodium content of commonly used salt supplementations

	Sodium content
1 tsp table salt	2000mg
Gastrolyte (oral rehydration solution)	240mg per sachet (based on 1 sachet per 200mL water)
Gatorade (sports drink)	280mg per 600mL bottle
1 tablet (600mg sodium chloride tablet)	240mg sodium

- **Pancreatic Enzyme Replacement Therapy (PERT) – Creon**:
    - The enteric coated microspheres are pH sensitive.
        - Protects the enzyme from the acidic environment of the stomach (activated in the alkaline environment in the duodenum).

Table 6.4. Creon dosage & administration recommendations

Doses based on lipase component:

INFANTS	CHILDREN/ADOLESCENTS
Creon: Creon micro (5000 International Units per scoop) Dose: ▪ 1 scoop Creon Micro per approx. 3-5g fat ▪ Starting dose approx. 5000 International Units / kg/day Administration: ▪ To be given on fruit puree/gel (i.e. apple puree) • Use the same type of puree each time so that the baby associates this with Creon	Creon: Creon 10,000 capsules (10,000 International Units per capsule) Dose: ▪ 1 Creon capsule per approx. 8-10g fat ▪ Doses exceeding 10,000 International Units/kg/day should be avoided due to risk of colonic stricture.

    - Families are taught one of two ways to dose Creon:
        - Fat counting – requires precision and includes label reading
        - Meal/snack doses – less precise but often enough to prevent malabsorption
    - Patients with appropriate Creon dosing/administration and ongoing signs/symptoms of malabsorption should be reviewed by the Gastroenterologist.
        - A proton pump inhibitor or H2 antagonist can be used to reduce the acidic environment of the stomach and improve the efficacy of Creon.
    - When assessing a patient's PERT regime it is important to consider:
        - Adherence
        - Dose and effectiveness of enzymes
        - Timing of enzyme administration – enzyme activity peaks at approximately 30minutes post ingestion and a split dose may be required.
    - Helpful hints/troubleshooting for parents & families:
        - Once opened spoon apple puree into an ice cube tray and store in the freezer.
        - Store enzymes in a cool dark place & avoid keeping them in the glove box of a car or on a window ledge as heat degrades the enzymes.

6.6 Vitamin Supplementation[1]

- CF patients, particularly PI patients at risk of fat soluble vitamin deficiencies. Supplementation is usually required to maintain adequate serum levels.
- Vitamin supplementation may be for maintenance or treatment of deficiencies

6.6.1 Maintenance of recommended daily intake levels

- Baseline supplementation begins from diagnosis in all PI patients.
- Pentavite or VitABDECK are usually recommended to maintain fat soluble vitamin levels.
- Serum fat soluble vitamin levels are measured at a minimum of annually in all patients.

Table 6.5. Recommended starting intake for fat soluble vitamins in CF

	Age	Requirement	Normal Serum Range	Treatment Threshold
Vitamin A	0-3yrs > 3yrs	1500-2000 International Units /day 2500-5000 International Units /day	0.8-2.5 micromol/L	0.8 micromol/L
Vitamin E	0-3yrs > 3yrs-7yrs >8yrs	40-150 International Units /day 150-300International Units/day 150-500 International Units /day	12-36 micromol/L	9 micromol/L
Vitamin K	0-3yrs > 3yrs	150-500 microgram/day 300-500 microgram/day	0.3-2.6 micromol/L	<0.3 micromol/L
Vitamin D	See section 6.6.2, Table 6.8 for details			

- **Important note:** The aim is for the above daily requirements to be met by a combination of dietary intake and vitamin supplementation, and not supplements alone.

Table 6.6. Recommended multivitamin preparations to achieve initial supplement doses

	Composition	Dosage (daily)
FOR CHILDREN 0-3years use Pentavite Infant plus Micel E		
Penta-vite Oral Liquid Infants 0-3years	***Important note:*** *Pentavite contains Vitamins A, B1, B2,B3, B6, C, and D3. It does not contain vitamin E.* Per 0.45mL: - 490micrograms RE as retinyl palmitate =1633 International Units Vitamin A - 10micrograms colecalciferol = 400 International Units Vitamin D	<12 months: 0.45mL 1-3 years: 0.9mL
Micel E	Per mL - 156 International Units Vitamin E	<12months: 0.5mL >12months: 0.5-1mL Dose may be increased where vitamin E is deficient with normal vitamin supplementation and additional vitamin A supplements are not required.

FOR CHILDREN 3-18years Use VitABDECK		
VitABDECK	*Important note: Vitabdeck contains Vitamins B1, B2, B3, B5, B6,B12, C, K* Per capsule: - 1.39milligrams Retinyl Palmitate, = Vitamin A 0.75milligrams= 2500 International Units Vitamin A - 11micrograms=440 International Units Vitamin D - 123.8milligrams d- alpha-tocopherol acid succinate=150 International Units Vitamin E	4-10 years: 1 capsule >10 years: 1-2 capsules
ALTERNATIVE MULTIVITAMIN PREPARATIONS:		
Bio-Logical Vitamin A, D and E Solution	Per mL; Vitamin A 2188IU Vitamin D 1000 IU Vitamin E 102 IU	0-12 months:0.7mL 1-3 years: 1mL 4-7 years: 1.5mL 8-18 years: 2mL
Centrum Kids	Per tablet: Vitamin A 1500IU Vitamin D 100IU Vitamin E 10units Centrum Kids is a multivitamin containing both water and fat soluble vitamins, and minerals.	Greater than 3 years: 1 tablet daily Centrum Kids is used if VitaABDEK is not tolerated and patients may require additional supplementation of individual vitamins in order to meet requirements.
ADDITIONAL SUPPLEMENTS FOR INDIVIDUAL DEFICIENCIES:		
Bio-Logical Vitamins A and E solution	Per mL - 1.2milligrams retinyl palmitate = 2210 International Units Vitamin A =663micrograms RE - 75milligrams d-alpha-topherol acetate =102 International Units Vitamin E	<12months: 0.5mL >12months: 0.5-1mL If child takes Pentavite,or Vitabdeck continue while supplementing for vitamin A & vitamin E.
OsteVit-D Oral Drops	For administration of doses of 200, 400, 600 or 800 International Units: Per 0.04mL drop: - 5micrograms colecalciferol = 200 International Units Vitamin D	See Table 6.7
OsteVit-D Liquid	For administration of dose of 1000 International Units or greater: Per mL - 125micrograms colecalciferol = 5000 International Units Vitamin D	See Table 6.7
OsteVit=D Tablets	Per tablet - 25micrograms colecalciferol = 1000 International Units Vitamin D	See Table 6.7

6.6.2 Treatment of fat soluble vitamin deficiencies:[1]

- Fat soluble vitamin deficiencies may result from:
  - Malabsorption, poor intake, liver disease, progressive lung disease & worsening clinical status, poor compliance to PERT or vitamin supplementation and any previous bowel resections.
- **Vitamin A & E**
  - Vitamin A and E are given to younger patients in liquid form
  - It is important to check levels 3 months after commencing replacement therapy as a guide to adherence and/or therapeutic response.
  - Excessive vitamin intake can be hazardous.
  - *Note higher dose supplementation may be required for a short period (3 months) to bring levels back within the normal serum range*
- **Vitamin K**
  - Vitamin K supplementation is guided by the gastroenterologist.
- **Vitamin D**[4]
  - Vitamin D levels are routinely performed as part of the annual review bloods.
  - Vitamin D levels should be maintained ≥ 50mmol/L.
    - Internal audit in 2012 showed that we achieve this in 85-88% of CF patients.
    - Recent US CFF recommendations suggest ≥75mmol/L, but until evidence is available describing improved outcomes, ≥50mmol/L will be the target
  - Because a nadir occurs during winter months, the vitamin D level should ideally be checked over the winter months.
  - Standard vitamin preparations (eg Pentavite & VitABDECK) contain some colecalciferol (vitamin D3) (see Table 6.6), however where levels are low use preparations containing colecalciferol alone in addition to standard or usual vitamin supplements.

Table 6.7. Current recommended Vitamin D Supplementation for different age groups[4]

Age	Routine intake (Achieved by supplementation from Pentavite/VitABDECK) (International Units)	Step 1 dose increases (International Units)		Step 2 dose increase (International Units)
		Add colecalciferol (vitamin D3):	Daily total:	Further increase colcalciferol to dose not exceeding total daily maximum (including Pentavite/VitABDECK):
Birth to 12 months	400-500	400-500	800-1000	Not > 2,000
>12 months to 10 yrs	800-1000	800-1000	1,600-3,000	Not > 4,000
>10 yrs	800-2000	800-2000	1600-6000	Not > 10,000

6.7 Dietary Management

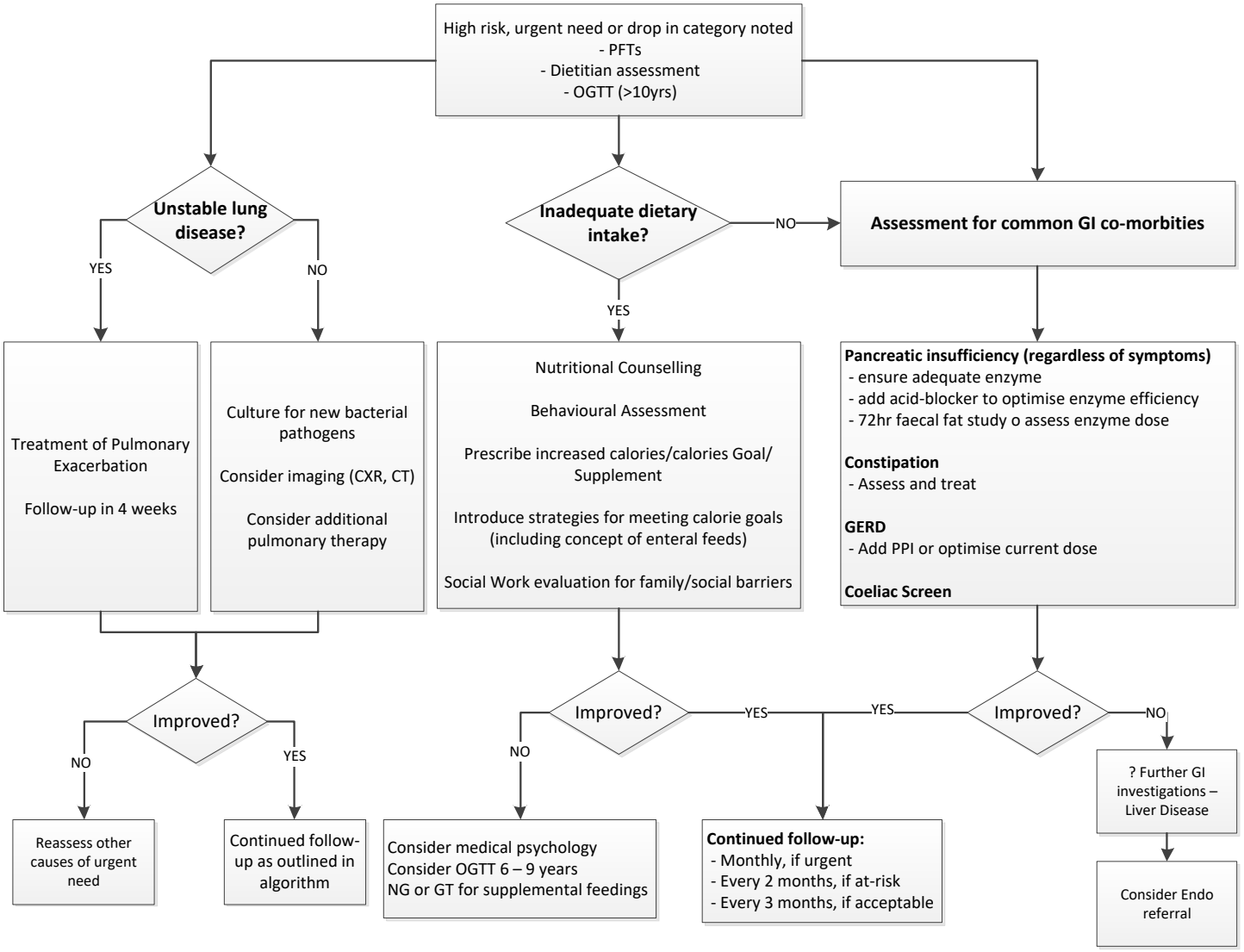
Patients falling within high risk and nutritional failure categories on screening are approached according to the algorithm in Figure 6.1.

- This is a guide only and managed with input from the entire multidisciplinary team
- Direction of dietary intervention will depend on the nutrition assessment and how the patient progresses through the nutrition care algorithm.

Points to consider include:

- Dietary quality
  - Quantitative assessment: Overall energy intake; macro and micro nutrient intake and/or
  - Qualitative assessment: Aim for a variety of foods from all 5 food groups. The CF diet is not a 'junk food' diet
- Food environment
  - The impact of pressure surrounding food intake/meal times
  - Working the 'CF diet' into the family diet
  - Potential negative impact of force feeding i.e. oral aversion to food long term
- Food behaviours
  - Normal fussy eating behaviours vs. fussy eating heightened by the pressure of the CF diet
  - The implementation of fussy eating strategies from a young age
  - Body image (particularly for adolescent girls)
- Nutrition counselling
  - Benefit of clearly communicated SMART goals at each review
  - Practical and clearly documented strategies to help achieve goals
- Screening & management of nutrition related co-morbidities
  - CFRD (OGTT, BSL control, insulin regime)
  - CFLD
  - DIOS (salt and fluid intake as well as Creon dose/compliance)
  - Other GIT issues (assessed in consultation with the gastro team)

Figure 6.1. Nutrition Algorithm for Paediatric Cystic Fibrosis Patients High Risk or with Urgent Nutritional Need



6.8 Oral and Enteral Nutrition Support

6.8.1 Goals of Nutrition Support

- Optimise growth: Improve weight gain, growth (aimed at meeting genetic height potential) and BMI centile.
- Improve and/or maintain nutritional status.
- Alleviate the pressure to meet elevated energy requirements via diet alone.
- Promote normal development and progression through puberty.

6.8.2 Oral nutrition support (ONS)

- Recommended for children/adolescents struggling to maintain adequate growth.
- Can pose as a financial burden to families & the high energy/high protein diet with fat fortification should first be optimised.
- Limited evidence to support benefit of use long term – taste fatigue is often reported.

6.8.3 Enteral nutrition support (ENS)

No current guideline recommending when to consider ENS but the following should be considered:

- Assessment for the presence of CF related co-morbidities (including coeliac screen & recent OGTT).
- Pubertal status: Where is the child/adolescent in relation to pubertal stage?
- Lung function: As the lung function declines, energy requirements are increased, particularly note whether the FEV_1 is <40-50%.
- Previous enteral nutrition: Has ENS been beneficial for weight gain in the past?
    - Minimum of 2 weeks of overnight NG feeds recommended prior to gastrostomy.
- PPI/H2 antagonist trial to optimise enzyme efficacy.
- Body Image and psychological status: is the lack of intake a result of depression or other concern.

Points to considering for ENS

- Aiming for 40-60% of estimated energy requirements from overnight feeds.
- Commencing & grading up feeds:
    - Feeds are commenced and graded up slowly usually over a period of 3-4 nights to prevent poor feed tolerance.
    - A patient on 237mL cans (i.e. Ensure Plus) will receive 1x can over 10hrs on night 1. Increase by 1 can each night until goal of 3-4 cans is reached.
- Reflux risk:

  - The bed should be elevated >30 degrees and rate limited for patients at significant reflux risk.
  - Consider PPI for patients on overnight feeds.

- Practicality for home:
  - Aim for cans (instead of powder feeds where possible).
  - Salt can be added to overnight feeds to help meet requirements.
  - Bolus feeds (i.e. 1x can of Ensure Plus) can be provided during the day while a patient is unwell and unable to maintain adequate oral intake.
  - Initially aim for feeds 7x nights per week with plans to reduce to 5-6x nights longer term.
- Creon:
  - Creon (given as a split dose pre and post overnight feeds based on total fat content per feed.
  - .
- Funding:
  - Variety funding: maximum 6 months
  - CHW CF clinic will currently refund ½ the cost of oral or enteral feeds for families when receipts are available
  - CF NSW: short term feed funding where possible

Table 6.9: Commonly used feeds recommended for ONS and/or ENS at CHW

		Calories	Additional
Young children (>12 months and 8 kg)	Nutrini Drink powder	1-1.5kcal/mL	Topping or nesquik can be added to vary the flavour *Used as an oral or enteral feed*
	Sustagen Kids Essentials powder	1-1.5kcal/mL	
	Pediasure tetras	1kcal/mL	Good addition to school lunchbox
Older children & adolescents (>25kg)	Ensure Plus (200mL tetra)	1.5kcal/mL	Good addition to school lunchbox
	Ensure Plus (237mL can)	1.5kcal/mL	The first choice for most new gastrostomy patients *Used primarily as an enteral feed*
	Jevity HiCal (237mL can)	1.5kcal/mL	Fibre containing feed *Enteral feed that is often used in conjunction with EnsurePlus for those children with constipation*
	TwoCal HN (200mL tetras or 1000mL bags for overnight feeds)	2kcal/mL	High calorie enteral feed used for adolescents who struggle to gain weight on 1.5kcal/mL overnight feeds

***Note** this list is not extensive and infants or children with allergies or gastrointestinal complications often require different feeds.*

6.9 The Newly Diagnosed Infant[1]

Breastfeeding:

- Encourage and support breastfeeding.
  Most infants with CF are able to maintain adequate growth while breastfeeding.
- The benefits of exclusively breastfeeding a CF baby for the first 6 months include a decreased use of intravenous antibiotics for the first 2 years of life (Australasian Clinical Practice Guidelines for Nutrition in CF, 2006).
- Energy supplements i.e. Polyjoule syrup, MCT Procal or MCT oil +/- concentrated infant formula top ups can be used as required.
- A standard infant formula is usually recommended where breastfeeding is not possible.

Pancreatic Enzyme Replacement Therapy (PERT)

- A 3 day Faecal Fat Test (FFT) is usually recommended prior to commencing PERT (refer to Gastrointestinal Management [section 5] for more details).
- All newly diagnosed CF infants with confirmed PI are commenced on Creon Micro Granules (1 scoop=5000 International Units).
- PERT is only commenced prior to the 3 day FFT results if the patient has obvious signs of malabsorption (frequent/oily stools) in combination with poor weight gain.
  The following should be considered when commencing PERT:
  - **Starting dose:** approx. 5000 International Units per kg.
    - Always work per ½ or full scoop i.e. ½ scoop prior to each feed for most newborns.
  - **Administration:** Give with a small amount of apple puree on a baby spoon.
    - Apple puree can be frozen in ice-cube trays with one cube to be defrosted daily.
  - If Creon beads aren't cleared from the baby's mouth post feed they can cause irritation/ulcers.

Salt

- All PI and most PS infants are commenced on salt supplementation at diagnosis after discussion with their treating physician.
  - **Starting dose:** ¼ teaspoon
  - **Administration:** Mixed with apple puree and given with enzymes for PI infants or dissolved into formula bottles or small amount of expressed breast milk for PS infants.

Fluids

- Importance of adequate hydration in CF discussed at initial education.
- General fluid requirements for infants are: 150mL/kg (0-6months) and 120mL/kg (6-12months).
  - Many CF infants will exceed these recommendations (especially if catch up growth is required).
  - Breast milk (or infant formula) alone is an adequate form of hydration for CF infants.

- Parents are not advised to give their infant additional fluids as water.
- Gastrolyte (or Hydralyte) may be used to help maintain hydration if an infant is unwell & not feeding (short term).
    - Can be administered in small volumes (age specific) via ORAL syringe during times of illness.

Vitamins

- Fat soluble vitamins (A, D and E) are check with routine bloods at the time of diagnosis.
- All PI and most PS infants are commenced on fat soluble vitamin supplements on diagnosis.
- Recommended starting doses: Pentavite Infant Drops 0.45mL and Micel E 0.5mL.

Education re normal infant feeding: Often done at follow up CF clinic appointments.

6.10 The Late Diagnosis

There are a number of things to consider and to be discussed with families of children who have a late diagnosis of CF including:

Growth:

- PI patients are often failing to thrive at the time of diagnosis. This is evident by serial weight measurements falling greater than or equal to 2 centile bands.

Dietary recommendations:

- The typical high fat and energy diet with PERT for PI patients are recommended from diagnosis.
- In most circumstances oral or enteral nutrition support is not necessary as a first line management.
- PI patients who are symptomatic as a result of malabsorption may find it difficult to implement the high fat CF diet.
    - Often have experienced abdominal pain and discomfort with high fat foods and therefore liberalising the diet can be challenging.
- Salt supplementation commenced at the time of diagnosis according to the appropriate age based recommendations.

PERT:

- Commencing toddlers and young children on enzymes can be challenging from a behavioural perspective.
- It is important to discuss strategies with families and enforce that the child is not to eat until they have taken their enzymes with either fruit puree (infants) or water (children).

Vitamins:

- Vitamin levels are to be assessed at the time of diagnosis and supplementation commenced accordingly.

6.11 Additional Resources

Additional resources on request from the Dietetics department:

- Factsheets
- Department CF Nutrition Handbook

6.12 Chapter 6 References

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7 Psycho-Social Management

- CF has a significant impact on the emotional and physical development of the child, young person and their family.
- The TIDES study is a recent multicentre study across 8 countries that investigated rates of depression and anxiety in >1000 adolescents and >2000 caregivers.[1, 2] It found that:
  - 25% of adolescents expressed depression and 20% expressed anxiety
  - 35% of caregivers expressed depression
  - Rates of 2-3 times the general population
  - Detrimental effects were seen on adherence and clinic visits

7.1 General Considerations

- **Emotions Experienced**
  - Throughout the course of the child's life, it is usual to expect that the child and adolescent with CF, their parents and perhaps other family members will experience a wide range of emotions.
  - These can include feelings of sadness, grief, anger, confusion, anxiety, fear, guilt and resentment.
  - Different family members may feel different emotions at different times, and each family member's reactions might change over time.
- **Religious and Cultural Beliefs**
  - A family's religious and cultural beliefs with regards to illness need to be considered.[3]
  - This may influence aspects such as their attitude to medical intervention, feelings about hospitalisation, and feelings about end of life care and death.
- **Relationship Issues**
  - CF may place enormous strain on relationships. It is vital that areas of potential conflict be identified immediately and possible solutions sought.
- **Family Issues**
  - CF impacts on family life. All family members need to adjust to the treatment demands of having a child with CF, and some may achieve this adjustment more readily than others.
  - Higher levels of distress and an avoidant coping style are associated with poor psychological outcome[4].
  - Support may be necessary for family members other than patient and parents.
- **Support Systems**
  - A family's available support networks influence their long-term adjustment to CF.
  - Low levels of family support are associated with poor psychological adjustment.[4]

- **Developmental Milestones**
  - Major developmental stages and transitions often pose a crisis for children with CF and their families and may precipitate the re-emergence of emotions such as grief and loss.
  - Ongoing assessment and psychological support are vital during these stages.
- **Childhood and adolescence**
  - The diagnosis and impact of living with CF has a significant impact throughout the lifespan.
- **Peer Relationships and Activities**
  - Consideration should be given to a child or young person's life outside the family, particularly with regard to school environment and peer relationships.
  - Many have problems with interpersonal relationships which can result in isolation and social maladjustment.[5]
- **Interaction with Hospital Staff**
  - Some families may feel they are constantly being "watched" and judged by health professionals.
  - Parents in particular need to be affirmed in their "expert" role with the child, and encouraged to actively participate in decision making with regard to treatment.
- **Adjustment Issues**
  - Sometimes children and adolescents with CF require individual counselling if they experience major periods of non-adherence, profound distress and difficulties adjusting to their illness.
  - Referral to the Department of Adolescent Medicine for assessment and support around adherence, adjustment, transition and family issues can be helpful.
  - In some instances families, children and adolescents may experience major psychiatric disorders.

7.2 Children and Adolescents

- CF may create a wide range of issues and feelings for children and adolescents.
- Some of these will be issues also common to children without CF.
- Living with a chronic illness interacts with normal development and increases the complexities of the issues that arise. These can include:
  - A feeling of being different from their peer group.
  - Difficulties balancing the demands of their illness with school, family and peer responsibilities.
  - Being self-conscious or embarrassed about their illness e.g. having to take enzymes, coughing etc.[6]
  - Concerns about falling behind academically due to frequent hospital visits or periods of hospitalisation.
  - Needing to follow an intensive daily treatment routine.

- Concerns about their future and their own mortality.
- Loss/death of friend/sibling or relative from CF.
- Concerns about the burden their disease places on their parents.
- Being jealous of their healthy siblings.
- Anxiety about medical procedures e.g. needles etc.
- Concerns about medical intervention and the impact this will have on their appearance (insertion of port and gastrostomy).
- Ongoing concern about what they eat and how much they weigh.
- Fear of complications e.g. CF related diabetes or liver disease.
- Issues relating to fertility, sex, drugs and alcohol.
- Fears, anxieties and dreams about what the future holds, including the potential negative impact of CF on future employment opportunities[7] and fertility.[8]
- Possibility of undergoing a lung/liver transplant.
- Peer group pressure around a range of normal or risky behaviours.
- The conflict between the need to be dependent when they are struggling for independence. Parents and adolescents are encouraged to develop a level of interdependence, acknowledging that the roles of parent and child are changing, but accepting that this will be a gradual change that occurs over extended time.
- Feeling of having no control over their lives.
- Feeling that decisions are made without their input e.g. by doctors, nurses, social workers, parents.

- It is important to realise that the CF team may overestimate the psychosocial impact of CF on an adolescent[9] emphasizing the importance of a structured assessment to clarify concerns.
- Non-adherence is a commonly encountered problem in CF, present in over 50% in one adult CF study.[10]
  - May be accidental or intentional, with simple forgetfulness reported as a common cause.[11]
  - Postulated reasons include inadequate knowledge, psychosocial resistance and educated non-adherence. [12].
  - For further information see Chapter 8.

7.3 Parents

- Parents with children who have CF may struggle at different times with different aspects of the disease and how it impacts on family life.
- Mothers may become overly involved and protective, leading to enmeshment, whilst fathers may be involved less leading to withdrawal.[13]
- Depression has been reported in 30-35% of mothers of children with CF.[1, 14] Decline in a child's health can lead to increased family stress.[13]

- Some of the issues encountered by parents may include:
    - A belief that the disease is somehow their fault, given the genetic component of CF.
    - Grief issues related to the loss of a "healthy child".
    - Continual vigilance around preventing their child from developing CF related bacteria e.g. *P. aeruginosa*, *B. cepacia*.
    - A belief that CF can be controlled e.g. by doing more physiotherapy, not allowing children to mix with peers.
    - Fear of the future and long-term implications of the disease.
    - Achieving a balance between being supportive and structured around their child's treatment however not being over protective.
    - Financial constraints compounded by the illness
    - The process of "letting go" i.e. handing over responsibility for management of treatment to their adolescent. (See note on interdependence in previous section).
    - Communication difficulties between parents.
    - Concerns regarding genetic counselling, further pregnancies and antenatal diagnosis
    - Balancing the needs of the child with CF and the needs of other family members.[15]
    - Disruption caused by clinic visits and periods of hospitalisation.

7.4 Siblings

- Chronic illness impacts on all family members.
- It is not unusual for siblings to experience struggles related to living with a person with CF, and it may be necessary to provide family support and intervention to assist in the resolution of such issues. These may include:
    - Feeling jealous about extra time and attention the sibling with CF requires.
    - Frustration with the restrictions CF places on family routines and lifestyle.
    - Feeling concerned about their sibling particularly at periods of deterioration
    - Feeling embarrassed about their sibling having Cystic Fibrosis.
    - Feeling confused about what is happening in the family, when other family members are distressed.
    - Confusion about health and illness, in particular, unintentionally seeing illness as the only way to gain attention in the family.

7.5 Grandparents

- Grandparents and extended family are also be affected by the diagnosis of CF.
- They may experience issues such as:
    - Feeling responsible and guilty that they passed on the disease.
    - Feeling isolated due to lack of current knowledge about CF.
    - Feeling fearful about minding their grandchild due to the treatment they require.
    - Feeling a strong sense of identification with their own child and the grief they may be experiencing.
    - Becoming over-involved and overly concerned about their grandchild.
    - Unintentionally creating conflict especially around issues of nutrition and physiotherapy, due to their lack of understanding about CF.
- In addition to the above, the presence of pre-existing personal, family and situational problems can be exacerbated by an illness like CF.
- The early identification of these issues and the prompt intervention by a social worker is therefore paramount.
- Grandparents can be very supportive and greatly add to the quality of the family system.
- To enable this to happen, involve them in CF education, attend clinic visits, learn physiotherapy techniques and become familiar with and reinforce the treatment routine

7.6 Referral for assessment

- A number of teams provide input to screen and manage psychosocial issues as they arise.
- CF social worker is closely involved with children and parents, from diagnosis, within the clinic structure and is the 1st line of review when concerns arise.
- From early 2013, the department of psychological medicine will be involved in the younger children (pre-adolescence). They will meet with families:
    - At the time of diagnosis
    - At the time of annual review
- This assessment will act as a screen for emerging psychosocial issues. The CF social worker will also be present during this process. Interim reviews will be arranged as necessary.
- In the older children (adolescents), annual review will be conducted by the CF social worker, and as required in between, based on concerns raised by the CF team and the child/family will be referred to the Adolescent Medicine Unit or to the Department of Psychological Medicine, when appropriate, as outlined below:

Adolescent Medicine Unit

- Issue of compliance and adherence
- Family distress and coping
- Minor mental health concerns, not deemed to require cognitive behavioural therapy or psychiatric medication

Department of Psychological Medicine

- Kids with severe disease likely to require lung transplant.
- Kids with complex social and /or mental health needs
- Kids outside Metro Sydney with complex psychosocial needs.

Prior to being seen by psychological medicine, the following must be provided or ensured for all referred adolescents:

- A clear mental health question articulated by the referring physician.
- Referral is made in consultation with the CF social worker.
- No other psychosocial team is currently involved that child/family to avoid undue replication (e.g. AMU, ICAHMS).
  - If another team are involved, there must have been adequate discussion, and endorsement of any planned referral.
  - There is an expectation that this team will liaise with CHW psychological medicine as well, during their period of involvement.
  - In specific circumstances CHW psychological medicine will review and hand back to the local services when appropriate.
- Reasons for referral have been discussed with the family and the family are willing to engage.

7.7 Medication options

- Whilst several medication options exist, the choice of medication, if indicated, should be made after discussion with Psychological medicine/AMU.
- Options include Selective serotonin reuptake inhibitors (SSRIs) such as Fluoxetine, which has the best available evidence base and is most widely used in adolescents.
- It is important to consider the use of medication in conjunction with other therapies or strategies which are additionally useful (e.g. cognitive behavioural therapy, family based therapy)
- Close monitoring for adverse events and response to therapy is essential
- Consideration of potential interactions with existing medication should also be considered.

Table 7.1 Anti-depressants Used in Adolescents

Note: These medications must be initiated and doses changed by an adolescent medicine specialist or child psychiatrist.

Drug	Initial Dosage	Preparations	Notes
Citalopram	10mg daily	Tablet 10mg Tablet 20mg	Considered second line Usually given in the morning May cause QT prolongation
Escitalopram	5mg daily	Tablet 10mg Tablet 20mg Oral solution 10mg/mL	Considered third line Usually given in the morning May cause QT prolongation
Fluoxetine	5mg daily	Dispersible Tablet 20mg Capsule 20mg	Considered first line Usually given in the morning Not recommended in liver disease
Fluvoxamine	25mg daily	Tablet 50mg Tablet 100mg	Give with food to reduce GI upset Usually given in the morning but sedation is a common side effect; if this occurs, give at night.
Sertraline	25mg daily	Tablet 50mg Tablet 100mg	Usually given in the morning. Dose reduction may be required in liver disease.

7.8 Chapter 7 References

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8 Adolescent Management Issues & Transition to Adult Care

8.1 Background

- Adolescence is characterised by rapid physical, cognitive, mental, emotional and social changes leading to the acquisition of adult roles and responsibilities.
- The tasks of adolescence are to establish a stable and realistic identity, achieve independence, to become comfortable with one's sexuality and to acquire skills for a future vocation.
- The time of adolescence represents heightened concerns for those living with the challenges of chronic illness.
- Generally adolescence is thought of as occurring in 3 stages:
    - **i.** Early (12-14 years)

      Adolescence involves coming to terms with the physical changes of puberty.
    - **ii.** Middle adolescence (15-16 years)

      Peer group becomes paramount as the young person struggles to become independent of parents and develop a sense of their own identity.
    - **iii.** Late adolescence (17-18 years)

      Involves defining functional roles in terms of work, lifestyle and relationships.
- Understanding the needs of adolescents and encouraging increasing self-management and adherence to CF treatment regimens are central to the care of adolescents.
- In this chapter the role of the CF team in the care of adolescents is outlined.
- Consideration is given to psychosocial concerns such as depression, which can complicate management as well as physical effects on growth and puberty, menstrual management and planning for successful transition to adult care.

8.2 Aims of Management

- To be conversant with:
    - The impact of chronic illness upon the adolescent
    - The effects of CF upon growth, puberty and mood
    - Sexuality, fertility and pregnancy in CF
    - The consequences of smoking
    - The implementation of a CF management plan in adolescence
    - Management of non-adherence with therapies
    - Transition to adult care with individualised management plan

8.3 Management Procedures

8.3.1 The impact of chronic illness on adolescents

- Developmental tasks of adolescence conflict with demands of having a chronic illness.
- Objective illness severity, perceived illness severity and psychosocial functioning has a variable relationship.
- Having a chronic illness can affect all areas of the young person's life: physical, psychosocial, family, school attendance and peer relationships.
- Overall, outcomes appear to be improved with management in specialised CF Centres[1] and recent studies reassuringly indicate improving prognosis for both males and females throughout adolescence. [2]

Physical Impact

- Adverse physical effects of CF can become more marked during adolescence related to deteriorating lung function, nutrition and the rapid changes of puberty especially if associated with non-adherence to treatment.
- Frequently seen effects include:
    - Growth delay; growth is slower but usually growth potential is achieved with optimised nutrition.
    - Pubertal delay; on average 1-2 year delay, however this is less frequently seen with optimal medical therapy and good nutrition. (1)
    - Chronic cough and decrease in exercise tolerance; more marked with exacerbations of suppurative lung disease
    - Increasing dyspnoea and fatigue
    - Pancreatic insufficiency with associated malabsorption and abnormal stool patterns more significant if poor adherence
    - Complications increase with age, e.g. CF related diabetes, osteoporosis, arthritis liver disease.

Psychosocial Effects

- Adolescents with CF have a demanding and time consuming treatment regimen which in itself can create a feeling of difference and isolation from their peers.
- Physical effects may exacerbate these feelings of difference and this may be dealt with by denial and non-adherence.
- Self-perceived health status may differ significantly from objective health status, and this may vary over time depending on individual, family and school related stressors.
- Establishing self-identity and independence may be more difficult due to:
    - Therapy requirements
    - Parental over protection

- Delayed puberty/growth
- Frequent hospital outpatient appointments and admissions

- Areas that foster independence, including peer relationships, school attendance and achievement, vocational training or part time employment may be adversely affected due to disease severity or demands of treatment.

Table 8.1. Impact of CF on development

Early Adolescence	Middle Adolescence	Late Adolescence
• Distortion of body image • Isolation from peers	• Enforced dependency. • Less acceptance by peers	• Reduced vocational options • Concerns about relationships and fertility

School

- Encourage and support regular attendance both as inpatient (attending hospital school) and outpatient
- Educate school community about CF using CNC school visits, fact sheets; especially important at times of change such as primary to secondary school.
- Liaise with school as needed to facilitate regular attendance/achievement
  - Advise regarding educational provisions through the Board of Studies for external exams, special access schemes for university entrance.
- Social interactions with peers are important and can be encouraged to facilitate normal adolescent development.

Family

- A supportive family environment is a key factor and a positive predictor of good adherence to treatment and appropriate psychosocial adjustment to illness.
- CF does however have an enormous effect on all families and the way they function with relationship strain, genetic implications for further pregnancies and variable effects on well siblings.

8.3.2 The effects of CF on growth and puberty

- Adolescents with CF who receive optimal nutrition have better growth, maintain better nutritional reserves and have better pulmonary function than patients with CF who have low weight for height.
- Conversely, being underweight correlates with growth failure, pubertal delay and increasing complications and inversely with survival.
- Management involves:
  - Restoring energy balance.
  - Treating specific nutrient deficiencies.
  - Appropriate pancreatic enzyme replacement therapy (PERT).

- Attendance at specialised multidisciplinary CF clinics with ongoing nutritional assessment and support can normalise growth.

- Consultation among the CF team between the Dietitian, Gastroenterology, Respiratory and Endocrinology subspecialists is most important if there are ongoing concerns regarding growth despite appropriate nutrition.
- Consider:
  - Address poor adherence to existing management strategies.
  - Supplemental feeds.
  - Gastrostomy feeds for appropriate weight gain.
  - Exclude other causes – assess glucose tolerance and treat CFRD as needed.

Pubertal delay:

- Puberty is associated with significant changes in growth and development requiring even higher caloric requirements for the adolescent with CF.
- Delayed puberty is defined as:
  - Absence of pubertal development by age 13 years in females and 14 years in males, or
  - Failure of developmental progression over a 2 year period.
- Reported to be common among adolescents with CF with an average of approximately 1 to 2 years delay in both males and females.
  - Related to under-nutrition, severity of lung disease and for some, use of systemic steroids.
  - Early diagnosis and optimal medical and nutritional support can facilitate normal growth and development.[2]
  - In Adolescent males, previous predictive models have been described: [2]
    - Weight <10th percentile + Height <25th percentile + FEV, <60% predicted had sensitivity, specificity and positive predictive value of 70%, 92% and 93% respectively.
  - Delayed puberty can also be seen as a surrogate marker reflecting increasing disease severity.
  - In Adolescent females, average age to menarche can be up to 2 years later among females with CF, especially those with low weight and significant deterioration in lung function.
    - Studies indicate however normal hypothalamic-pituitary-gonadal axis and normal menarche and cycles are usually achieved.
    - Delayed puberty has been linked CFRD during adolescence and homozygous F508del genotype
  - Recent data suggests this may not be the case in current CF cohorts.[3, 4]

- **Management and further assessment:**
    - Optimise all medical and nutritional treatment including adherence to PERT (non-adherence can be used as a weight control measure for those with body image disturbance).
    - Consider nutritional support – such as oral supplementation or gastrostomy feeds.
    - Consider more intensive therapy for respiratory exacerbations e.g. admit for more regular "tune-ups".
    - Assess hormone levels, bone age, BMD.
    - Endocrine review if indicated.
    - Early intervention can help to avoid the psychosocial sequelae[5] of delayed puberty with altered body image and feeling different to peers.

8.3.3 Menstrual Management

- Once menarche occurs the majority of girls with CF achieve normal or near normal menstrual cycles[5] although the incidence of menstrual problems is high.
- Primary amenorrhoea
    - Usually seen in context of pubertal delay, severe lung disease and under-nutrition.
- Secondary amenorrhoea and/or oligomenorrhea
    - Can occur related to exacerbations of chronic chest infection, weight loss or difficulties maintaining nutrition.
- Discussion around sexuality, safe sex, fertility and of pregnancy is important.
    - Studies indicate that adolescents and their families would like discussion by the CF team around 14 years.
- Young women with CF usually begin sexual activity at the same age as their peers.[6, 7]
- Dysfunctional uterine bleeding
    - Can occur spontaneously particularly in the first year after menarche, however it is important to consider whether there are exacerbating or precipitating factors present. e.g. drug side effects, liver impairment or bleeding diathesis.
- Vaginal thrush can be a common complication of antibiotic management and effectively treated greatly improves quality of life.
- Stress incontinence with coughing:
    - 47% of adolescent females with CF reporting symptoms in one study.[8]
    - Routinely checked by CF physiotherapists with appropriate exercises and intervention provided.
- If any of the above issues occur referral to the Adolescent Gynaecology Clinic run in Adolescent Medicine or consultation with Adolescent Medicine for further assessment is appropriate.

8.3.4 Sexuality, fertility and pregnancy

Sexuality

- Studies indicate similar levels of sexual activity among young people with CF as compared with other youth[8]. Young people with CF, however:
  - were less well-informed
  - had lower rates of contraception
  - had higher rates of STD
- This highlights the need for accurate information regarding:
  - puberty and fertility
  - contraceptive methods/STDs
  - risks of pregnancy
  - thorough medical and psychological guidance regarding planned parenthood.

Fertility in Females

- Rates of infertility in CF women are not as high as in CF men, with up to 50% being able to conceive a child.[9]
- Fertility issues may arise owing to several factors: [10]
  - Thickened cervical mucus
    - May not thin sufficiently at the time of ovulation (impaired ability to increase its degree of hydration). Sperm may consequently struggle to penetrate through the cervical os.
  - Delayed menarche
  - Ovulation irregularities – may be secondary to low body weight or chronic inflammatory state.
  - Uterine fluid also requires a high bicarbonate content to facilitate egg fertilization.
- Contraception should be discussed and considered for all women with CF irrespective of disease severity. [6]

Pregnancy

- Encourage informed decision-making and provide appropriate support around medical, social and ethical issues.
- Women who achieve pregnancy tend to have better lung function, were less likely to be homozygous DF508 and had earlier diagnosis.[11]
  - Majority of pregnancies had good outcomes. Live term births occurred in 67% of pregnancies involving male CF partners and 74% of those involving CF women.
- Recent Australian data also provides favourable outcome data and an outline of a collaborative obstetric and CF management approach.[12, 13]

- Pregnancy optimally should be planned with thorough clinical evaluation pre-conception to adequately assess risk to both the mother and foetus:
    - Lung function – monitor regularly with optimal anti-infective therapy. With the predicted normal decrease in total lung capacity in the last trimester an estimate can be made as to whether respiratory insufficiency would occur.
    - Nutritional status maintenance.
    - Check glucose metabolism; avoid systemic steroids if possible.
    - Avoid drugs known to be a problem for the foetus during pregnancy and lactation
    - *B. Cepacia* and multi-resistant organisms if present may be associated with increased risk of deterioration in lung function.
- Nutritional assessment and advice prior to conception is associated with greater maternal weight gain and heavier babies.
    - Maternal outcome post-partum is directly related to nutritional status during pregnancy.
    - Consider oral supplementation or NGT feeding if nutrition is an issue.
- **Good outcomes** for mother and infant can be achieved with careful planning and monitoring of the pregnancy by an active obstetric and CF team collaboration.

Fertility in Males

- Majority of males with CF have azoospermia, but do have normal sexual potency.
    - Azoospermia is related to a developmental defect of Wolffian duct-derived structures leading to absence, atrophy or obstruction of the vas deferens, part of the epididymis, and the seminal vesicles.
- The CFTR gene causes abnormal secretion of electrolytes and water by the epididymal epithelium disrupting the optimal fluid environment for sperm maturation and transport.
- Particular genotypes may be associated with mild disease presenting in an older age group with male infertility.[14]
- Treatment of male infertility is possible using microsurgical epididymal sperm aspiration (MESA) together with in-vitro fertilisation and intra-cytoplasmic sperm injection (ICSI) has produced good results. [15]
    - Prior screening of the partner for the common CF mutations is also advised.
- Discussion of infertility with adolescents with CF is a sensitive issue and is usually part of the process of the young man seeking appropriate understanding of his illness and planning his future which frequently occurs in late adolescence.
- Age 14 years is indicated by parents and adolescents when they would like the CF team to discuss these issues; providing reassurance and guidance regarding fertility options and investigations as indicated or at a later date.

8.3.5 Contraception in CF: Choice of OCP[16, 17]

The choice of oral contraceptive pill is guided by two factors – the dose of oestrogren required and type of progestogen.

For the majority of patients, oral contraceptive pills containing doses of 20micrograms ethinyloestradiol or 30micrograms ethinyloestradiol are effective. Monitor effect according to the following markers and increase if required:

- low to suppressed LH and FSH (if clinically well with reasonable body weight).
- light to absent periods and no breakthrough bleeding.
- thin endometrium on pelvic ultrasound.

OCPs containing newer progestogens eg. drospirenone may have a better side effect profile as they are less androgenic and may improve acne. OCPs with drospirenone appear to have slightly elevated risk of VTE but this remains much lower still than VTE risk of pregnancy itself; however these OCPs are not on the PBS.

Consider PBS availability in choosing the brand of OCP prescribed.

OCP may be contraindicated with:

- significant liver impairment
- long-term central venous access or
- significant family/individual contraindications.

Table 8.2 Combined Oral Contraceptive (COC) Preparations Used in Adolescents

Trade Name	Oestrogen Component	Progestogen Component	Notes
Low dose			
Femme-Tab 20/100, Loette, Microgynon 20, Microlevlen	Ethinyloestradiol 20mcg	Levonorgestrel 100mcg	ONLY Femme-Tab brand is PBS subsidised Low dose preparations have a higher incidence of break-through bleeding than standard dose.
Yaz	Ethinyloestradiol 20mcg	Drospirenone 3mg	Not PBS subsidised Drospirenone has anti-androgenic activity. It is thought to be beneficial for acne and hormone-associated emotional imbalance, though evidence is lacking. Risk of VTE is greater than for levonorgestrel or norethisterone.
Standard dose			
Brevinor, Norimin	Ethinyloestradiol 35mcg	Norethisterone 0.5mg	All brands are PBS subsidised Both brands are also available in preparations containing 1mg norethisterone (Brevinor-1 and Norimin-1).
Femme-Tab 30/150, Levlen, Microgynon 30, Micronelle, Monofeme, Nordette	Ethinyloestradiol 30mcg	Levonorgestrel 150mcg	All brands are PBS subsidised
Marvelon	Ethinyloestradiol 30mcg	Desogestrel 150mcg	Not PBS subsidised Desogestrel has less androgenic activity than levonorgestrel or norethisterone containing COCs, but higher risk of VTE.
Isabelle, Yasmin	Ethinyloestradiol 30mcg	Drospirenone 3mg	Not PBS subsidised Drospirenone has anti-androgenic activity. It is thought to be beneficial for acne and hormone-associated emotional imbalance, though evidence. is lacking. Risk of VTE is greater than for levonorgestrel or norethisterone.

The 50micrograms ethinylestradiol which is on PBS may still be used:

- if there is inadequate response to lower dose preparations
- in patients who are currently stabilised on it with no adverse effects such as nausea, breast tenderness or bloating
- if there is a tendency to miss pills (under this circumstance alternative contraception should be considered)
- if the patient has a higher body weight

Limited data available do not support its routine use as pharmacokinetic data (old) appear similar in normal and CF subjects.

Note: A higher oestrogen dose OCP (start with 35 micrograms ethinyloestradiol) may be required due to frequent or continuous antibiotic therapy.

Interactions: CYP3A4 inducers decrease the efficacy of OCPs. eg.rifabutin or rifampicin. The dose may need to be adjusted these situations, including a higher progestogen dose. One approach is to take 2 tablets of 30micrograms ethinyloestradiol + 150micrograms levonorgestrel.

DepoProvera should not be used as it is associated with osteoporosis.

For patients requiring hormonal treatment for low bone mineral density and who do not require contraception, consider use of oestradiol valerate with a progestogen.

8.3.6 Depression

- Young people with CF may become depressed secondary to their illness or unrelated to their illness.
- It is important that all health care professionals feel confident to diagnose and assess depression with appropriate referral for ongoing management.

Importance of diagnosing and assessing adolescent depression

- Age group with highest prevalence rates for depression
- Continuities with adult depression
- Links with suicide in the young
- Increased uptake of health damaging lifestyles
- Adverse effects on adolescent development

Prevalence

- At any one time, between 1 and 3% of adolescents suffer from a major depressive disorder
- Up to 24% of young people will have suffered at least one episode of major depression by the time they are 18 years old
- Between 15 and 40% of young people report symptoms of depressed mood and depressed symptomatology [18]

Features of depression

- Persistent sadness or volatile mood
- Feelings of helplessness & hopelessness
- Irritability, withdrawal, persistent boredom
- Low energy, poor concentration
- Changes in eating or sleep patterns

- Deteriorating school performance
- Increased risk taking; alcohol & drug abuse
- Frequent complaints of physical illness

When to refer a depressed adolescent for further assessment and therapy

- Serious risk of self-harm
- Unsupportive environment
- Failure to respond to initial treatment
- Markers of bipolar disorder or other psychiatric condition

Assessment of self-harm / suicidality

- Have you ever thought that life was not worth living?
- Have you ever wished you were dead?
- Have you ever thought about hurting/killing yourself?
- Have you ever tried to hurt/kill yourself?
- Do you plan to hurt/kill yourself now?
- How do you plan to hurt/kill yourself?

Increasing hierarchy of concern

- IDEA – fleeting
- IDEA – persistent, intrusive
- PLAN – fleeting, poorly thought out
- PLAN – persistent, more systematic, comprehensive

Assessment following attempt

- Is suicidality still present?
- Is there a disorder to be treated?
- Is there a predicament to untangle?

Features enhancing resilience

- Attached to a caring adult/supportive family
- Independence and competency e.g. part time job, household chores
- High aspirations with adult support
- Effective schooling – supportive, stimulating.

8.3.7 Smoking in CF adolescents

- By age 15yrs: 30% females, 23% males — are recent smokers (i.e. within the last month)

- Smoking among young people remains of concern. [19]
    - 6% of 12–19-year-olds reported smoking daily in 2007: 2% of 12–15-year-olds, 6% of 16–17-year-olds, and 13% of 18–19-year-olds smoked daily.
    - 16–17-year-old females were twice as likely as their male counterparts
- Onset of smoking needs to be considered amongst adolescents with CF, especially those previously well, presenting with increasing respiratory symptoms or deterioration in pulmonary function tests.
- Exploration of the link between smoking and increased symptomatology and assessment of other individual, family and school-related issues will be helpful to enable the most appropriate intervention.
- If the young person sees himself or herself as having a 'well' chronic illness it is not a disincentive to smoking and they may respond to peer pressure in the same way as their healthy peers.
- Smoking may be an indicator of other problems:
    - Anxiety
    - Depression
    - Other 'at risk' behaviours (alcohol, drug use)
    - Body image/weight concerns
- Smoking is associated with:
    - Parental smoking status (i.e. one or both parents smoke)
    - Peers who smoke
    - Lower parental education/Social economic status
    - Poor school performance
- HealthCare Providers can play a VITAL role.
    - "Smoking as a vital sign" – ask about it
    - Opportunistic **brief intervention** can be effective – **The 5 A's**: [14;15]
        Ask – about smoking
        Advise – to quit
        Assess – stage of change
        Assist – set a date
        Arrange – follow-up
    - Educate to prevent
    - Encourage to quit
- Education/Behaviour Change *alone* 5-10% cessation rate
  plus Nicotine replacement therapy 10-20% cessation rate
  } At 12 months
- For further information go to the Smoking Cessation intranet page.
- To access Smoking Cessation e-Learning Training go to: http://intranet.schn.health.nsw.gov.au/education-and-development/e-learning

8.3.8 CF Management plans in adolescence

Planning Management

- Assess severity (e.g. biological, physiological, functional, burden of illness)
- Assess psychosocial development (HEADSS assessment)
    - Home
    - Employment/Education/Exercise
    - Activities
    - Drugs
    - Sex, Suicide/self-harm/Sleep
- Enlist collaboration from adolescent and family

Communicating management

- See the adolescent alone- after seeking permission from parents
- Engage the adolescent – take the time to know about their life
- Explain the treatment in developmentally appropriate and clear language
- Keep treatment simple. Give direct concrete instructions (verbal & written)
- Invite feedback from the adolescent
- Discuss with the family

Encourage and support management

- Although the structure of clinic has changed to minimise cross infection risks adolescent specific CF clinics are run at key times throughout the year to facilitate meeting the adult CF teams and facilitate transition to adult care.
- Regularly assess and direct self-management in preparation for independent management and transition to adult care.

8.3.9 Adherence to treatment

- CF imposes a demanding treatment regimen from the time of diagnosis and usually becomes more intensive with increasing age.
- Adherence is difficult to assess, however there is a spectrum from complete adherence to non-adherence. Majority demonstrating incomplete adherence.
- Establishing structure and routine around treatment plans help but there is great variability between adherence rates to different components of therapy. e.g. both parents and children report better adherence to medication than to chest physiotherapy or dietary recommendations.
- Flexibility within the family and for the adolescent at some stages or with some aspects of the treatment regimen is associated with better overall adherence.
- Increasing severity may be associated with improved adherence, as the consequences of non-adherence become greater with deterioration in health.

- Causes of Incomplete adherence:
  - Long term need for complex and demanding treatment i.e. no end point for treatment cessation
  - Lack of awareness of importance of adherence to particular treatments
  - Family disorganisation
  - Emotional resistance e.g. depression or anxiety
  - Failure to see or feel an immediate improvement.

  For some, an informed and considered decision that treatment is worse than the illness.

Table 8.3: Factors associated with adherence to treatment.

Factor	Positive	Negative
Developmental	Adolescence; may be positive or negative.	
Medical factors	Severity; may be positive or negative.	
Cognitive/emotional motivational factors	Knowledge. Positive attitude. Positive self-esteem. Autonomy.	Emotional disturbance e.g. fear, guilt, shame, depression, anxiety.
Action of family	Positive family climate. Open relationships in family. Family cohesion. Parental support.	Family conflict. Behavioural problems e.g. avoidance behaviour. Strict control. Negative feedback.
Action of peers	May be positive or negative.	
Relationship with health care providers	Supportive and motivating the patient to be actively involved in care. Treatment as a part of normal daily routine. Encouragement. Positive feedback.	Conflict between adolescents and health care providers.
Patient education	Based on individual needs. Achievable goals. Goal setting with adolescents. Behaviour centred interventions.	Number of visits (unsure effects).

- Knowledge linked to attitude and behaviour change is associated with improvements in
  - Adherence
  - Health outcome
  - Doctor/patient satisfaction

Management of Non-Adherence

- Accept reasonable degrees of adherence to avoid conflict, guilt and a sense of failure i.e. prioritise around aspects of treatment and build on this.
- Develop a therapeutic alliance i.e. young person and caregiver work together to explore underlying reasons for non-adherence. Be empathic, enthusiastic, supportive, non-critical and understanding.

- Consider psychological, social and physical factors contributing to non-adherence.
- Explore educational aspects, attitudes and beliefs surrounding illness to enable behavioural change to occur.

Protocol for Management of non-adherence

- *Explore general issues (HEADSS)*
- *Explore beliefs and expectations around treatment*
- *Give verbal and written information*:
  - ❖ Give clear expectations of outcome; benefits of therapy; use goal setting
  - ❖ Simplify treatment regimen, integrate treatment with daily activities
  - ❖ Involve young person in aspects of decision making e.g. appointment making
- *Frequently monitor progress; encourage & motivate*
- *Know when to seek help (individual and/or family counselling)*

Preparation for transition to adult care

8.3.10 Transition to Adult Care

See SCHN Transition Care intranet for resources i.e. transition plan, self-management checklists.

For Transition Planning on PowerChart go to ad-hoc charting and select transition planning.

- Successful transition from paediatric to adult care is a process not an event and as such is a long term goal for the CF team
- Transition involves a planned collaborative process centring on the young person, their family, the paediatrician and adult CF teams supported by the general practitioner or local physician and Trapeze, the specialist transition service of The Sydney Children's Hospitals Network (SCHN).
- An individualised transition plan is developed for each young person with CF as they progress through adolescence so that they move onto adult care with confidence.
- Identify a member of the clinical team to coordinate and monitor the transition plan.
- At age 14 refer young person to Trapeze to ensure an effective and successful transition. Trapeze support young people with chronic conditions through to adulthood and ensure engagement with adult services is maintained
- The transition process is supported by the CF team and Clinic processes, which aim to specifically meet the developmental needs of adolescents.
  - From age of 12 onwards - encourage young people with CF to start to see CF physician and other team members alone bringing parents back to the consultation as appropriate.
  - Evaluation of the transition program indicated young people and their families valued meeting the adult CF team at clinic, ongoing support with information and having their 1st appointment organised.[20]
- At set times throughout the year clinics focussing on transition issues occur to facilitate moving on to adult care and enable preparation for transition to adult care.
- Joint clinics between paediatric and adult specialists is encouraged to improve communication and ensure a seamless transfer to adult care.

PREPARATION PHASE: 12 years and onwards

- Adolescent friendly environment optimal
- Smaller clinic numbers so more time to see both adolescent and family members
- Actively promotes and encourages the acquisition of self-management skills (see self-management checklist on Transition Services intranet page and on powerChart transition planning). The checklist assesses knowledge about the condition, communication skills and understanding and use of medications. It also highlights problem areas where further input by various team members may be required (e.g. nutritionist, physiotherapist, psychologist).
- At age 14 refer young person to Trapeze for specialist transition support. Go to adhoc charting and select Trapeze Service and select Referral Form.
- Provides consultation/liaison with Adolescent Medicine regarding general medical, adjustment and psychosocial issues as needed (see Chronic Illness Referral Form) and referral to CHiPS (Chronic illness Peer Support) where appropriate
- Provides consultation with Psychological Medicine around emerging psychiatric comorbidity.

ACTIVE PHASE: 16-18 years

- Timing of transition to adult care is flexible according to the individual needs of the adolescent. In general, at the end of high school (i.e. 18yrs) when:
    - Growth and pubertal development are completed.
    - Cognitive developmental tasks of adolescence are usually completed with young person now planning and making future-oriented decisions.
    - Can choose adult clinic geographically suited to University, College and employment choices
- Once the young person reaches the age of 16 years, a transition plan, including end of life plans if appropriate, must be completed. Other tools, such as checklists, which help in assessing the young person's ability to manage their care, may be used to start discussion around transition planning.
- CNC or consultant facilitates individualised transition plan for each young person using Transition Checklist.
- Ensure that the young person has a GP, as the GP will play a pivotal role in their ongoing care. The GP is often the single health professional who is constant during this period of change and can provide a wealth of support to both the young person and the family.
- Provides introduction to **adult physicians/CNC's** who attend CF transition Clinics throughout the year to meet young people preparing to move to adult care.
- All allied health groups involved with the young person's care need to ensure that comprehensive referrals are made to all relevant parties.

Transition Map

Diagnosis up to 12 years

- **GENERAL CF CLINIC**

12 years onwards

PREPARATION PHASE

- **Self-management skills**, education and evaluation
- A member of the clinic team allocated to coordinate transition
- **Consultation/liaison** regarding general health issues/psychological issues
- **CNC Transition** to facilitate management across paediatric/adult services and develop an individualised transition plan.
- Transition planning on PowerChart commenced.
- At age 14, referral to Trapeze is made for specialist transition support.

16 – 18 years

ACTIVE PHASE

- Individualised transition plan is implemented
- CF Clinic provides 3 clinics per year to focus on transition with **adult team attending**, plus individual **transition plan discussed with young person**.
- Adolescents receive detailed information of adult services (CF Clinic, Trapeze, GP/Physician pamphlets) a year prior to transition.
- **Visit chosen adult services** and meet staff if possible.
- Return to paediatric service to **discuss any concerns** prior to transition.
- Transition planning on PowerChart regularly updated and discussed.
- **Standardised transition referral letter** sent.
- **Formal transition** to adult service. First appointment planned and made by young person with CNC.
- Country patients need an *additional* referral to local adult physician to liaise with adult CF Clinic.

Adult CF Clinic

INITIAL APPOINTMENT ATTENDED

18 – 19 years

EVALUATION

- **Follow-up** with adult teams re engagement with regular appointments and progress either by letter or at regular inter-clinic CF team meetings in consultation with Trapeze.
- Questionnaire: young person, parent, adult physician/CNC.

8.4 Chapter 8 References

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9 Outpatient Management

9.1 The CF Clinic

- The CF Clinic runs twice weekly:
  - Monday evening (4:30-7pm)
  - Wednesday morning (8.30am – 12pm)
- CF physicians are timetabled to share these clinics between them.
- An indefinite referral is required from each patient's local doctor for the respiratory and gastroenterologist providing ongoing CF care. *If a patient's local doctor changes this referral needs to be updated to reflect this*.
- An adolescent specific CF clinic occurs on the fourth Wednesday each month and is attended by the Endocrine Physician and often adult CF service providers.
- We encourage families where possible to make their next clinic appointment before leaving clinic and update any changes to family contact details.

Cross infection measures whilst at the Clinic

- To minimise cross infection risk all patients are allocated their own clinic room on arrival and the staff review the patient in this room.
- The Lung Function Laboratory staff call patients directly from their rooms for PFT testing thus minimising patient contact in the laboratory area.
- Appointment times need to be strictly adhered to in order for the clinic to be able to provide individual patient rooms.
- Families are encouraged to bring their own toys and entertainment to prevent patients sharing toys.

The CF Clinic comprises a Multidisciplinary Team:

- CF Physicians:
  - Respiratory
  - Gastroenterology (Wednesdays only).
  - Adolescent
  - Endocrine (third Wednesday only)
- Nursing [CNCs are hospital based, however, they visit homes as well]
- Clinic Coordinator
- Physiotherapists
- Social Worker
- Nutrition & Dietetics Staff
- Research Team
- Administrative Support Staff
- Pulmonary Function Laboratory Staff
- Pharmacist

9.2 Frequency of Attendance

- The city patients usually attend clinic a minimum of every 3 months.
- Rural and regional intercity patients may attend less frequently, seeing their local paediatricians in between visits to clinic, which are at least 6 monthly.
- At each clinic appointment the patients:
  - See their physician.
  - Have a sputum specimen collected by the CNC.
  - Are reviewed by other members of the clinic (e.g. allied health workers) as indicated.

9.3 The Annual Check

Annual Check

The annual (or interval) check is performed at the visit closest to the child's birthday. This check involves:

- **Consultation with:**
  - ❖ Respiratory Physician
  - ❖ Gastroenterology Physician
  - ❖ Nutritionist
  - ❖ Physiotherapist
  - ❖ Social Worker
- **Pulmonary Function Tests:**
  - ❖ Spirometry for children 5 years or older.
  - ❖ Plethysmography for children aged 8 years or older
  - ❖ Multiple Breath washout for pre-schoolers and above
    Not in those where FEV_1 known to be <60% predicted
- **Allergy Skin Prick Test at age 5yrs**
- **Sputum Sample**
- **Blood Test to assess:**
  - ❖ Full Blood Count, Renal function and electrolytes, and IgE
  - ❖ Liver Function Tests
  - ❖ Vitamin Levels (A, D and E)
  - ❖ Blood Sugar Level
- **Modified glucose tolerance tests:**
  - ❖ if aged over 10 years (or if clinically indicated, see section 11.1.3)
  - ❖ Subsequent referral for Oral glucose tolerance test as indicated based on the results
- **Imaging:**
  - ❖ Chest X-Ray
  - ❖ Chest CT scan [*Routinely performed at age 5-6 years and age 10-12 years, or as clinically indicated]*
  - ❖ Bone mineral densitometry – at entry to adolescence and at transition. If abnormal then every 1-2 years.
  - ❖ Liver Ultrasound [every two years if noted to have hepatomegaly or if persistently elevated liver enzymes]
- **Shwachman score** (measure of overall severity)

9.4 Shwachman Score

This score forms part of the child's Interval Check, and is divided into 4 sections:[1]

General Activity	
5	confined to bed or chair
10	rests a great deal dyspnoea after minimum effort poor school attendance
15	often rests during the day, tires easily after exertion fair school attendance
20	lacks endurance, tires at end of day good school attendance
25	normal activity, regular school attendance
Physical Examination	
5	severe coughing tachypnoea and tachycardia signs of R heart failure marked clubbing
10	frequent productive cough moderate pulmonary disease moderate clubbing, crepitations
15	occasional cough mild pulmonary disease slightly elevated respiratory rate early clubbing
20	rare coughing minimal pulmonary disease normal resting respiratory rate
25	no cough clear lungs, no chest deformity normal respiratory rate
Nutrition	
5	marked malnutrition, protuberant abdomen rectal prolapse large frequent fatty stools
10	ht and wt below 3rd centile abnormal stools abdominal distension, flabby muscles
15	ht and wt above 3rd centile abnormal stools poor muscle tone with reduced mass
20	ht and wt at 15-20th centile stools slightly abnormal
25	ht and wt above 25th centile well formed stools
Chest X-Ray	
5	extensive changes obstructive pneumonia and infection lobar atelactasis / bronchiectasis
10	moderate emphysema widespread areas of atelactasis /infection minimal bronchiectasis
15	mild emphysema patchy atelectasis increased bronchovascular markings
20	early emphysema minimal accentuation of bronchovascular markings
25	clear lungs fields

9.5 Weekly Team Meeting

A weekly team meeting is held every Tuesday in the research building conference room:

- 11 – 11:30am: **Discussion of current CF inpatients**
  - Directed by the registrar/fellow to allow a problem-orientated discussion regarding management.
- 11:30 – 11:40am: **Free discussion**
  - Enables nursing and allied health to have individual discussion with the physicians about specific problems or concerns.
- 11:40am – 12:30pm: **Outpatient discussion**
  - Directed by a rotating chairperson who is a member of the CF team.
  - CF physicians present their annual checks with discussion of any problems.
  - Input from allied health
  - Scoring of CXR and further management plans are formulated.
  - Discussion of patients presenting to outpatient clinic in the week following.
- 12:30 – 1:00pm: **Presentation**
  - Rotated between either a Business meeting, Journal club session, or Allied health/Nursing/Medical team presentation
  - According to clinic plan organised by Clinic Coordinator, Visitors or agenda items can be forwarded to the Clinic Coordinator.

9.6 Day Treatment Centre

- CF Treatment Centre is located in The Children's Hospital Medical Centre, ground floor, suite 4.
- Established as a central management facility for outpatients with CF.
- It operates Monday to Friday 8am to 5pm
- Staffed by the CF Coordinator and CF Nurse Consultants who liaise with the CF Fellow and other members of the CF team.

The aims of the CF Treatment Centre are to:

- Decrease presentations of non-urgent cases to the hospital emergency department
- Offers a preferable location to CF clinic, for acutely unwell patients to be seen thus preventing cross infection within clinic.
- Decrease inpatient length of stay by increasing access to Home Intravenous Antibiotics
- To provide an alternative location to home for routine procedures such as sputum collection and flushing of venous access devices
- To provide resources and education material for patients and their families.
- Family friendly environment for new patient education.

9.7 Referral

- Medical or allied health staff can make referrals.
- Self-referral is encouraged.
- Appointments MUST be made prior to attending either the outpatient clinic or the CF treatment centre.
- To make an appointment phone the CF nurse consultant on page via switchboard.

9.8 Chapter 9 Reference

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10 Endocrine Management

10.1 Cystic Fibrosis Related Diabetes Mellitus (CFRDM)

10.1.1 Background

- CFRDM is a distinct form of diabetes mellitus (DM), different from either type 1 or type 2 DM, but with shared features of both. [1]
- The primary cause is a relative insulin deficiency related to destruction of pancreatic islets. Insulin resistance is also reported in association with decreased clinical status.
- There are unique factors in CF, not commonly encountered in other forms of DM, which influence glucose metabolism: [1]
    - Malnutrition
    - Acute and chronic infection
    - Glucagon deficiency
    - Malabsorption
    - Abnormal intestinal transit time
    - Liver dysfunction
    - Increased work of breathing and elevated energy expenditure.
- Some treatments used in CF can also precipitate glucose intolerance such as corticosteroids and immunosuppressants (e.g. tacrolimus).
- Improved survival in CF has led to increasing numbers of adults with CFRDM. [16.9% of patients over 13 years of age require chronic insulin therapy (2003 US CF foundation patient registry report (n=21,742, 117 centres)].[2]
- Prevalence of CFRDM increases with age, now the most common comorbidity affecting patients entered in the CF foundation Patient Registry in the US.
- Oral glucose tolerance test (OGTT) is considered to be the gold standard for diagnosis of CFRDM.
- Categories proposed (Table 11.1), are based on the classification criteria of the American Diabetic Association (ADA), with additional modification:
    - CFRDM has been divided into those with and without fasting hyperglycaemia.

      Treatment in both these groups has been shown to be beneficial[3] so may not always be necessary to distinguish.
    - Indeterminate glycaemia (INDET) as an additional category. [3]

      Normal baseline and 2 hour glucose level but have a mid-point glucose peak of >11.1mmol/L.
- Odds of developing diabetes were 11 times greater in children (6 – 9yr olds) who had abnormal glucose tolerance (OGTT category IGT or INDET).[4]
- ADA criteria are based on the blood glucose concentrations above which intervention has been shown to prevent diabetic complications.
- Corresponding level for prevention of pulmonary deterioration and increased mortality is not yet known for CF, hence the modified classification system.

Table 11.1: Oral glucose tolerance categories in Cystic Fibrosis[6]

Category	Fasting plasma glucose before test (mmol/L)	Plasma glucose 2 hours post 1.75g/kg glucose (mmol/L)
Normal glucose tolerance (NGT)	<5.6	<7.8
Indeterminate Glycaemia (INDET)	<5.6	< 7.8 with a mid-point peak >11.1
Impaired glucose tolerance (IGT)	<5.6	7.8-11.1
CFRDM without fasting hyperglycaemia	<5.6	≥11.1
CFRDM with fasting hyperglycaemia	≥5.6	OGTT not necessary

- A spectrum exists ranging from normal glucose tolerance, increasing glucose intolerance, to CFRDM without fasting hyperglycaemia (FH) to CFRDM with FH.
- Whilst a general trend for intolerance to frank CFRDM with FH occurs, fluctuation may be seen.
    - A single abnormal OGTT may not indicate the need for treatment but simply highlights those with impaired glucose tolerance and the need for closer monitoring especially during infection.
- The OGTT result may vary over time.
    - In a recent 4 year prospective study, deterioration of OGTT category occurred in 22% and improvement occurred in 18%.[5]
    - In another prospective study 58% of those with IGT had normal subsequent OGTT results.[6]
    - Varying insulin resistance with clinical status may be responsible for the above variation.[7]

10.1.2 Prevalence

- Prevalence depends on definition of CFRDM used, and differs between centres.

Table 11.2. Prevalence of CFRDM in a large CF clinic where routine annual screening (by OGTT) has been recommended since the early 1990's in those ≥ 6yrs old:[8]

Age (years)	CFRDM (%)
5 – 10	2
11 – 17	19
≥ 18 ≤ 29	40
≥ 30	45 – 50

Risk factors for CFRD:[9]

- Increased age
- Female gender
- Pancreatic insufficiency
- ∆ F508 homozygous genotype
- Lung function – FEV_1 <70%, more frequent exacerbations (≥3/year)
- Impaired nutrition / growth
- Liver disease

- It is important to realise that type 1 DM has also been reported in CF.[9]

10.1.3 Screening

- CFRDM is often insidious in onset.
- Symptoms are a poor method of screening.
  - In adult studies, the majority were asymptomatic.[6]
  - In one paediatric population, only 2.7% were clinically recognised as having CFRDM, but on OGTT testing of 94 asymptomatic adolescents (aged 10-18 years), 17% had IGT, and 13% had CFRDM without FH.[10]
  - Abnormal glucose tolerance was almost exclusively found in those with pancreatic insufficiency and severe (class 1-3) CF mutations.[10]
- Symptoms, if present, can include:[11]
  - Polyuria and polydipsia
  - Failure to gain or maintain weight despite optimal nutritional support
  - Poor growth velocity
  - Unexplained decline in pulmonary function or increased exacerbation frequency
  - Failure to progress normally through puberty
- HbA1c is a poor screening tool for CFRDM
  - Adult studies have shown this value is frequently in the normal range,(6) possibly due to increased red blood cell turnover.[12]
- Whilst the OGTT is considered the gold standard method for diagnosis, it is not always practical to screen the entire CF population[11] and thus criteria for performing OGTT may need to be used.

Protocol for CFRDM screening at CHW:

Referral for a formal OGTT should be based on the following:

1. Patients ≥10yrs old will be screened annually in CF clinic using a modified glucose challenge test which involves:

- Non fasted BGL (capillary) to be checked. If >7.8mmol/L refer for OGTT, if ≤7.8mmol/L, give an oral glucose load of 1.75mg/kg (to max 75g) to be consumed in <5mins.
- Fast for 1 hour
- Check BGL (capillary), if >7.8mmol/L book for a formal OGTT

2. All patients will be monitored by annual measurement of a random plasma glucose as part of their interval check bloods. If abnormal (≥7.8mmol/L), refer for a formal OGTT.

3. In all CF patients admitted for acute pulmonary exacerbation requiring IV antibiotics, capillary BGL (fingerprick) should be measured by glucometer as outlined below:

- *All patients > 5 years:* pre and 2 hour post prandial finger prick BGLs taken on the ward for the first 48 hours of admission.
- *Continuous overnight feeds:* additional BGL measured during or immediately after the feed.
- *Abnormal glucose tolerance (7.8-11.1mmol/L):* finger prick tests continued during admission until instructed to stop by the CF team.
- *If BGL >11.1mmol/L:* continue to test 2 hours post prandially. Referral for endocrine consultation should occur, to evaluate the need for insulin therapy during the admission.

NB: Those with persisting abnormal BGL (≥7.8mmol/L) during an admission for acute pulmonary exacerbation should be booked for a formal OGTT, as part of their review 1 month post discharge.

4. Patients receiving 3 months or more of daily oral steroids in a calendar year.

5. Clinical suspicion of CFRDM based on symptoms as listed above.

Follow up after a patient has had a formal OGTT should be as follows:

- *OGTT normal:* continue annual screening as above.
- *IGT or INDET:* a period of home monitoring BGL's for 2 – 4 weeks.
  - Referral to endocrinology should be made if patient also has unexplained weight loss and lung function decline.
  - If home monitoring normal: repeat OGTT in 12 months (unless clinically indicated sooner).
  - If persistently elevated BGL's: refer to Endocrine for review and advice.
  - Continuous glucose monitoring system (CGMS) may be beneficial in some patients.
- *CFRDM:* refer to Endocrine for review and advice.
- Period of home glucose monitoring should be considered in those patients where strong clinical concern remains despite a normal OGTT[15].

- An audit of CFRDM diagnosed on OGTT, since the introduction of this screening protocol (August 2009), has recently been completed:
  - 10% of 10 – 18yr olds have been diagnosed with CFRDM.
  - While this screening protocol has identified more patients than the previous approach used at CHW, the incidence remains less than that of other published clinics, mentioned previously.
- An ongoing review will determine its ability at effectively identifying patients with glucose abnormalities.

10.1.4 Treatment with Insulin

- Therapeutic role for insulin in CFRDM with FH is clear.
  - Clinical status and pulmonary function may decline up to 4 years prior to diagnosis of CFRDM with FH, and insulin therapy has been shown to reverse these changes if given during this pre-diabetic period.[13]
- Insulin therapy is now recommended for CFRDM without FH in the updated ISPAD Clinical Practise Consensus Guidelines.[14]
  - Beneficial effect of insulin on BMI in CFRDM without FH has been reported in a recent multi-centre study.[15]
- IGT: evidence does not currently support routine insulin treatment.
  - Insulin should be considered on a case by case basis, after evaluation of lung function and nutritional trends, in conjunction with a period of monitoring and review by a paediatric Endocrinologist.
- Other treatment options are limited.
  - Main treatment approaches used in type 2 DM, such as oral hypoglycaemics, weight loss and diet control, are not recommended in CF.
- The CHW policy for insulin treatment is shown on the next page.
- Basal bolus regimens (short acting insulin prior to main meals with long acting in the evening) remain the gold standard for diabetic care.
  - Allow maximal flexibility with life commitments and variation in food intake.
  - However it is also the most intensive regimen.
  - In CF children already on a number of treatments, taking up a considerable amount of their daily schedule, it has the potential to destabilise compliance, with potentially catastrophic effects.
  - An individualised approach should be considered in patients where compliance issues have been previously identified, as well as younger children, and those whose insulin requirements are related to corticosteroid use for the treatment of ABPA.
  - A unified approach, agreed between specialities, including specialised CF and diabetic dietitians, is essential.
- For those with post-transplant medication induced DM (eg corticosteroid or tacrolimus induced), a modified approach to the insulin regime is often necessary.

Policy for Insulin treatment in CFRDM

1. Diabetes as outpatient (no glucocorticoids)

- Insulin detemir commencing pre-breakfast at 0.1units/kg/day, and dose titrated in 1 unit increments, to reduce postprandial (Target: 6-8mmol/L) and preprandial BG (target: 4-6mmol/L)
- Insulin detemir given, instead, at night for those on overnight feeds.
  - ❖ Check at 4 hrs after commencement of feeds and at end of feeding for titration
- If hypoglycaemic (<4mmol/L) during the day and hyperglycaemic pre-bed, then use twice daily insulin detemir; split the dose of insulin detemir to 2/3 morning and 1/3 evening, and titrate as outlined above.
- If fasting hypoglycaemia develops and postprandial hyperglycaemia persists, then reduce insulin detemir and introduce prandial insulin: 0.5 units rapid acting insulin (eg. Novorapid) per 15g carbohydrate.

2. Diabetes as outpatient (on systemic glucocorticoids)

- Insulin detemir commencing at 0.2 units/kg/day, and dose titrated in 1-2 unit increments, to reduce postprandial (Target: 6-8mmol/l) and preprandial BG (target: 4-6mmol/L)
- Insulin detemir at night for those on overnight feeds, with BGL checks at 4 hrs after commencement of feeds and at end of feeds to guide titration
- Twice daily insulin detemir if needed (as above) and prandial insulin if needed (as above)

3. When to add prandial or short acting insulin

- If fasting hypoglycaemia develops and postprandial hyperglycaemia persist, then reduce insulin detemirand introduce prandial insulin: 0.5 units rapid acting insulin (eg. Novorapid) per 15g carbohydrate
- If HbA1c >7%.

4. Diabetes as inpatient

- Insulin detemir commencing at 0.2units/kg/day, and dose titrated in 2 unit increments, to reduce postprandial and preprandial BG
- Will often need a second dose of insulin detemir 12 hours later if BG very high (>15mmol/L), i.e. BD insulin detemir in hospital titrating to target BG
- insulin detemir at night for those on overnight feeds, with BGL checks at 4 hours after commencement of feeds and at end of feeds for titration

5. When to add a correction dose

- In hospital if BG still >15mmol/L 4hours after first insulin detemir dose.

6. Recommendations for BG monitoring:

- As an outpatient, at least three times per day at different times to measure preprandial, postprandial and fasting to determine maximum insulin effect.
- For patients on night-time feeds in addition to above, test 4 hours post commencement and at end of feeds.
- As an inpatient, test pre-meals and pre-snacks and 11pm and 3am.

10.1.5 Recommendations for Nutritional Management

- Good growth is associated with improved long term outcomes for CF patients.
- Normal growth in this population may be difficult to achieve due to a combination of a number of factors including high energy requirements, malabsorption and inadequate calorie intake.
- Dietary management of these patients should be individualised depending on their nutritional status, dietary intake, glycaemic control and medication regimens.
- A high calorie, high fat diet is a key aspect of CF management. Restriction of caloric intake is not recommended.
- As recommended in the ISPAD Clinical Practise Consensus Guidelines[14], priority should be given to maintaining the CF diet as follows:
    - 120-150% of normal caloric intake for age
    - 40% of total energy from fat
    - 45-50% of total energy from Carbohydrate
    - No restriction of refined sugars (see note below)
    - Adequate fibre particularly in well-nourished patient
    - High protein intake
    - Unrestricted salt intake

Note: Where the patient has a high intake of refined carbohydrate products between meals, modification of carbohydrate intake with regard to timing and amount will be considered. To ensure maintenance of an adequate calorie intake, dietary modification with addition of high fat products will be encouraged.

Dietary advice

- Avoid high caloric drinks
- Spread carbohydrates over the day

Role of the CF Dietitian

- Liaison with the Endocrinology team to ensure the recommended insulin regimen matches eating behaviour and carbohydrate load.
- Manage the nutritional aspects of care, providing dietary counselling on maintenance of adequate energy intake in the context of achieving good glycaemic control.
- Provide education about the effect of food and carbohydrates on blood glucose levels, treatment of hypoglycaemia and the importance of regular carbohydrate intake throughout meals and snacks.
- In patients on multiple daily insulin injections or an insulin pump, to assess and provide further education about sources of carbohydrates, carbohydrate portions and adjusting insulin to match dietary carbohydrate intake.

10.1.6 Recommendations for Physiotherapy

- Advise patients to perform moderate aerobic exercise for at least 2.5 hours per week.[3]
- Patients will be educated on safety considerations with exercise.
- Consider monitoring BGL's pre and post exercise to monitor response.
- Modify the intensity/mix of exercise based on BGL response.
- Fast-acting carbohydrate snacks should be nearby during and after exercise.
- Patients with recurrent hypoglycaemia - recommend CHO snack pre-exercise.
- Ensure adequate hydration and salt supplementation.
- Select insulin injection site away from areas used during chosen form of exercise.
- Delayed hypoglycaemia can occur up to 24-36 hours post exercise as muscles re-fuel.
- When unwell BGL's and response to exercise can be impacted.[16]

10.1.7 Monitoring for long-term complications of CFRDM

- Comprehensive data on diabetic complications in CF patients with CFRDM is not yet available, but will become more apparent as survival continues to improve.
    - Similar rates of retinopathy to type 1 diabetes (27%), related to the duration of diabetes, and nephropathy in over 30% of non-transplanted CF patients have been reported in a small case series.[17]
- At present, screening for long term complications is recommended every two years following diagnosis of CFRDM.
- This is co-ordinated through the Department of Endocrinology.

10.2 Bone Disease

10.2.1 Background

- CFTR is expressed in human bone which suggests a role of CFTR in bone formation[18].
- The increased survival achieved with CF over the past 30 years has led to increasing recognition and prevalence of bone disease in CF in both adults and children.[19]
- Low bone mineral density has been shown to be prevalent in paediatric CF patients, and correlated to markers of disease severity such as pulmonary function and nutritional status.[20, 21]
    - Reported in 34% of children and adolescents despite normal nutritional status and mild lung function abnormalities.[22]
- Multifactorial pathogenesis of low BMD includes:

- Decreased levels of bone-forming osteoblasts and increased levels of bone-resorbing osteoclasts. [23]
- Low vitamin D levels[20], possibly due to: [24]
  - Poor sunlight exposure
  - Decreased absorption as a fat soluble vitamin, or accelerated catabolism)
  - Impaired gastrointestinal calcium absorption
  - Chronic lung inflammation
  - Side effects of CF treatments (e.g. corticosteroids)
  - Poor growth and delayed puberty.

- Increasing evidence that low bone mass may be associated with increased fracture risk in healthy children, typically from late adolescence onwards [25] but this has not been studied in detail in CF.
  - The data for fracture risk in younger children is conflicting describing either normal or increased risk in those with moderate lung disease.[26]
- Bone gain during puberty is also smaller in CF subjects compared to the normal healthy population and [27,28] the decreased peak bone mass accumulation achieved may explain the gradual BMD decline seen from late adolescence.[26]

10.2.2 Diagnosis and screening

- Dual-energy radiograph absorptiometry (DEXA):
  - X-ray can detect osteopenia (ribs, vertebrae) and complications (kyphosis, rib and vertebral crush fractures), but Dual-energy radiograph absorptiometry (DEXA) is a more sensitive screening and diagnosis tool for low BMD.
  - Z-score, the number of standard deviations (SD) the BMD is above or below age / height matched control subjects, is used as a guide to evaluate for the presence of decrease bone mass in children.
  - T-score, reflecting SD variation of peak bone mass, is used more commonly in adults and should not be used in paediatrics.

Protocol for screening for CF related Bone Disease:

All adolescents are screened at entry to adolescence with DEXA scans.

- If this is normal then a DEXA is repeated prior to transition to the adult services, unless clinical concerns arise in the interim.
- If this is abnormal the patient is monitored 1 – 2 yearly with DEXA scans.

- **Definitions**
  - Osteopenia is defined as a Z-score below -1.5
  - Osteoporosis is defined as symptomatic osteopenia i.e. those with a low bone mass and recurrent fracture and/or bone pain.
  - In adults the risk of fractures doubles for each SD below normal[29] but such correlations are not as convincing in the paediatric literature.
- Vitamin D levels are measured annually and should ideally be checked during winter, with the aim of maintaining adequate levels (25-hydroxycolecalciferol >50mmol/L).

10.2.3 Treatment

- Data is lacking for the management of bone disease in CF.
- General measures to maintain BMD include:
  - Maximising exercise, particularly weigh bearing physical activities
  - Good nutritional status including adequate dietary calcium and vitamin D on age
  - Optimization of lung function
  - Minimisation of corticosteroids.
- Calcium and Vitamin D:
  - To achieve the calcium and vitamin D requirements children will often require dietary supplementation.
  - Consult dietician for the recommended dietary intake of calcium and assessment of the child's current dietary intake. Daily supplementation is typically calculated by subtracting dietary intake from RDI.
  - Vitamin D content of currently used multivitamins is discussed in Chapter 6.
  - Children with CF often require much higher doses of vitamin D supplementation if absorption of fat soluble vitamins is impaired.
- Bisphosphonates:
  - Children with symptomatic bone disease may require oral or intravenous bisphosphonates.
  - Intravenous bisphosphonates have been shown to increase mineralization in adult CF patients with bone disease,[30] and confirmed by subsequent Cochrane review.[31]
  - Oral bisphosphonates have also been shown to be effective.[32]
  - Important side effects of treatment include hypocalcaemia, flu-like symptoms and bone pain.
  - The indication for use of bisphosphonate therapy is recurrent fracture/pain with low bone mineral density.

10.3 Chapter 10 References

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11 Palliative Care

Refer to separate guideline – Cystic Fibrosis – Palliative Care – CHW.

12 Cross Infection Guidelines

The following section outlines the recommendations of the "Infection Control Guidelines for Cystic Fibrosis Patients and Carers 2012".

12.1 Background Information

- These guidelines aim to prevent transmission between patients and their carers by reducing the risk of contact with respiratory secretions.
- Information about acquisition and transmission of organisms in CF is incomplete, and whilst these guidelines reflect "current best practice", guidelines change over time as new information emerges.
- Good hygiene is important in reducing infection from all kinds of bacteria.
- Pathogens of note include:
  - Most common bacterial pathogens (*S. aureus* and *P. aeruginosa*).
  - *H. influenzae*, particularly in young CF patients.
  - Members of the *B. cepacia* complex
  - Methicillin-resistant *S. aureus* (MRSA)
  - Respiratory viruses.
- *B. cepacia* complex species have been the most studied, serving as prototypes for infection control amongst CF patients.[1-3]
- Risk factors for acquisition of *B. cepacia* complex:
  - Attendance at school camps/education program/groups
  - Close social contact
  - Kissing
  - Intimate contact
  - Prolonged car rides
  - Fitness class
  - Sharing eating and drinking utensils
  - Sibling with *B. cepacia* complex
  - Handshaking
  - Inpatient exposures
  - Recent hospitalisation
  - Sharing room or bathroom facilities with B. cepacia complex infected patient
  - Sharing respiratory therapy equipment
- As patients survive longer and receive more powerful antibiotics, other micro-organisms are being isolated in sputum with increasing frequency, including: [4]
  - *Stenotrophomonas maltophilia*
  - *Achromobacter xylosoxidans*
  - *Ralstonia picketti*
  - *Pandoraea apista*
  - *Inquilinus limosus*
  - *Aspergillus fumigatus*
  - *Non-tuberculous mycobacterium* (NTM)
- These are environmental micro-organisms, found in water, soil and on plants, including fruit and vegetables.
- Whether all have a pathogenic role in CF lung disease and are capable of transmission between patients remains unclear.

12.2 General Guidelines

12.2.1 Methods of transmission[5]

- Most organisms are spread predominantly by contact or the droplet route.
- Transmission between CF patients may occur by a combination of different routes (i.e. both contact and large droplet methods) and therefore attention to all areas of potential transmission is important.
- Infection control precautions protect both CF health care workers and patients.

12.2.2 Hand hygiene

- Most important practice for preventing transmission is proper hand hygiene between patient contacts and when hands are contaminated with respiratory secretions, from either direct patient contact, or contact with patient equipment or soiled surfaces.
- Alcohol based hand rubs have greater efficacy compared with hand washing using soap and water or antimicrobial soap, and are the preferred hygiene agents.[6-8]
- When hands are visibly dirty or contaminated with body fluids, washing with soap and water is preferred.

12.2.3 Advice for patients and carers

- Always cover mouth and nose when cough or sneeze, preferably using a tissue.
- Wash hands frequently, including tips of and in between fingers, particularly if you cough a lot.
- When using toilet/bathroom facilities, wash hands with soap for 10-15 seconds and dry them thoroughly.
- Wash hands before eating.
- Do not leave sputum pots uncovered.
- Throw tissues away immediately after use.
- Avoid spa pools.
- Wash and dry fresh fruit and vegetables before eating.
- Additional advice for contact with other people with CF:
    - Do not share respiratory equipment (nebulisers, masks)
    - Do not eat or drink using the same utensils as other people with CF
    - Do not share drink cans, cups or bottles between people with CF
    - Do not share toothbrushes or towels
    - Do not share rooms with other people with CF if staying overnight
    - Refrain from shaking hands with other people with CF
    - Avoid dancing, hugging, or kissing other people with CF
    - Do not sit on each other's bed in hospital
    - Keep a distance of approximately 1 metre apart from each other when socialising
    - Be especially careful when you have a cold or flu like illness

12.3 Outpatient Clinics

- General hygiene guidelines should be observed as outlined above and relate to all hospital staff, patients and their carers, particularly after contact with respiratory and oral secretions.
- Alcohol based hand rub must be freely available in clinic rooms.
- Children are encouraged to cough into paper tissues, and tissues should be freely available in the clinic.

12.3.1 Standard and transmission based precautions

Table 13.1. Outline of Precautions for potential pathogens in CF

Type of Precaution	Potential Pathogens
Standard (Handwashing)	Applicable to all CF patients, independent of their clinical state and microbiology test results.
Contact	Bacteria ▪ *B. cepacia* complex species ▪ MRSA

12.3.2 Hand Hygiene

- All patients are educated in the use of hand hygiene.
- Alcohol based hand rub must be freely available in clinic rooms, waiting areas, and the respiratory function laboratory.

12.3.3 Gowns / Gloves

- Gloves and gowns should be used when contact precautions are observed and the health care worker is in direct contact with the patient (Table 13.2.).
- Both gloves and gowns should be removed after exposure and before providing care to another patient.

Table 13.2 Recommendations for use of hand hygiene, gloves and gowns

	Entering patient area	Close contact*	Aerosol generating procedures†
Hand hygiene	√	√	√
Gloves	x	√	√
Gowns	x	√	√

** when in physical contact with the patient, environmental surfaces or equipment.*

† aerosol generating procedures include nasopharyngeal aspiration, suctioning or nebulisation.

12.3.4 Segregation Standard

- Patients with *B. cepacia*, MRSA and clonal *P. aeruginosa* strains should be segregated in separate rooms in CF outpatient clinic from other patients with CF, and avoid mixing in open clinic areas or the respiratory function unit.
- Segregation is observed in time and/or space.
- These patients should come at the end of clinic, be placed immediately in single rooms, and be visited by the team in a separate room.
- They should not mix with general clinic patients.
- Our current CHW clinic structure complies with these recommendations. Routine clonal testing is only performed when clinically indicated (see section 4.4.4.).

12.3.5 Respiratory Function Testing

- Patients with MRSA or *B. cepacia* are segregated for respiratory function testing and "flagged" in advance so respiratory function unit (RFU) laboratory staff are aware of their presence.
- Spirometry is performed by the RFU laboratory staff in the clinic room that the patient is segregated into, using portable spirometry equipment, apart from on annual review visits when, due to the necessity for plethysmography, the patient is brought to the RFU laboratory at the end of clinic, once testing for the other patients have been completed.
- Please see the Department of Respiratory Medicine Policy and Procedure Manual for more information.

12.3.6 Toys/Sweets

- Patients and families are told to bring their own toys and discouraged from using common items in the waiting area.
- Families who allow patients to use common items must be aware of the risks involved.
- Sharing of toys (especially for young children who put toys in their mouths) is discouraged.
- Studies have shown that shared jars of sweets and lollies are sources of infection.

12.3.7 New Patients

- Patients who are attending a CF outpatient clinic for the first time are required to have a sputum test or airway specimen taken one week before attendance (include testing for *B. cepacia* and MRSA) to avoid casual introduction of new organisms to the clinic.
- This particularly applies to patients from overseas.
- If in doubt or no sputum is available then the patient should be segregated as for MRSA or *B. cepacia* until their status known.

12.3.8 Group Sessions

- Group sessions can be of benefit to participants but are generally discouraged.
- Consideration should be given to room size and to ensure that there is adequate ventilation.

- General hygiene rules, as above, are observed.
- People with *B. cepacia* and MRSA are not included.

12.3.9 Current Approach at CHW CF outpatient clinic

- As of 2012, CF patients in the CHW outpatient clinics are completely segregated and seen in individual clinic rooms.
- Wednesday am clinics are structured in two waves (8:30am-10am, and 10am-12pm), with rooms cleaned in between. Monday evening clinics have a single wave of patients attending (4:30-7pm).
- Patients are brought through to the RFU laboratory by RFU staff, to manage patient flow and prevent mixing in communal areas.
- MRSA and *B. cepacia* complex patients are tested in the RFU laboratory at the end of clinic or portable spirometers are taken to the individual clinic room.
- At present routine testing for clonal *P. aeruginosa* strains is not performed.
- Following measurement, RFU equipment is cleaned as per current guidelines.
- Acutely unwell patients are not seen within the outpatient clinic. Appointments are made for review in the CF treatment centre.

12.4 Inpatients

- General hygiene guidelines should be observed as outlined previously and relate to all hospital staff, patients and their carers. These rules are to be observed particularly after contact with respiratory and oral secretions.
- Ideally the patient's sputum culture result, particularly with regard to MRSA and *B. cepacia*, should be known prior to their visit to hospital to ensure the correct approach.
- The following section outlines the current approach at CHW.

12.4.1 Standard and transmission based precautions

- As outlined for outpatients in Table 13.1.

12.4.2 Hand Hygiene

- All patients are educated in the use of hand hygiene.
- Alcohol based hand rub must be freely available in patient rooms, and the RFU laboratory.

12.4.3 Gowns / Gloves

- As outlined in section 13.3.3.

12.4.4 Room Sharing

- CF patients should ideally have single rooms with their own washing facilities.
- If this is not possible, prioritise CF patients with *B. cepacia* complex species, MRSA in single patient rooms with their own facilities and isolate them as per hospital isolation precautions.

- Clonal *P. aeruginosa* strain testing is not routinely performed at CHW and only if clinically indicated (see section 4.4.4.).
- Patients with *B. cepacia* complex species must be nursed in a single room, even if this means transferring to another ward.
- CF patients should avoid sharing double, 4 or 6 bed room with other CF patients.
- CF patients should not visit rooms or sit on the beds of other CF patients on the ward, particularly if they are having physiotherapy or nebuliser treatment.
- If group activities are allowed patients should observe personal hygiene (e.g. sitting apart one metre, care in coughing etc).
- All CF patients who are heart, lung or liver transplant recipients are to be placed in a single patient room in accordance with hospital policy.
- CF patients with MRSA or *B. cepacia* are usually looked after on Variety ward or alternatively in isolation cubicles on other wards.
- Patients are considered free from *B. cepacia* or MRSA if it has not been cultured from sputum or grown from swabs on 3 consecutive occasions and over a year has lapsed since last isolated.
- For those patients under contact or droplet precautions, the door of the room may remain open unless potential aerosol-generating procedures, such as nasopharyngeal aspirates, suctioning or nebulisation, are being performed.

12.4.5 Chest Physiotherapy / Gym

- All patients are segregated for physiotherapy both on the ward and in the gym.
- If this is not possible, it is recommended that patients with *B. cepacia* and MRSA should be segregated from other patients with CF in these settings.
- See above section on gloves and gowns for their use during physiotherapy.

12.4.6 Patient equipment

- Equipment should be dedicated to a single patient to avoid sharing.
- If common equipment is unavoidable then adequate cleaning and disinfecting must be performed before use by another patient.

12.4.7 Patient transport

- Transport of patients under contact precautions should be limited to essential purposes.
- If the patient is transported out of the room, precautions should be maintained to minimise the risk of transmission of micro-organisms to other patients and contamination of environmental surfaces or equipment.
- When moving around outside of their room, patients with contact precautions should wear a face mask at all times. Other departments should be informed in advance of visit.

12.4.8 Socialising in Hospital

Hospital school

- Chronically colonised *P. aeruginosa* CF patients can attend school, but must maintain usual hygiene standards (sit 1m apart, care with coughing, contact).
- Patients not yet chronically colonised with *P. aeruginosa* can attend as normal, but must take particular care with other CF patients, particularly if colonised.
- MRSA patients are not allowed to attend. School work should be delivered to their room, unless special arrangements are made to attend alone out of school hours.
- *B. cepacia* patients can attend hospital school if no other CF patients are attending.

Starlight room/Bear Brasserie/Radio Bedrock

- Patients with MRSA and *B. cepacia* are not allowed to attend.

12.4.9 Respiratory Function Testing

- Respiratory function testing on inpatients should not occur at times when other CF patients are attending.
- Appointments for testing should be made with the RFU laboratory staff.
- Patients with MRSA or B. cepacia are segregated for respiratory function testing and "flagged" in advance so RFU laboratory staff are aware of their presence.
- Spirometry is performed by the RFU laboratory staff in the isolation room of the patient, using portable spirometry equipment.
- If this is not possible, it is essential that the patient should attend the RFU laboratory at a time when other CF patients or susceptible patient groups are not attending, to prevent transmission.
- Please see the Department of Respiratory Medicine Policy and Procedures Manual for more information.

12.4.10 Utensils / Food

- The general hygiene rules for sharing utensils and food are to be observed.

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13 Miscellaneous Associated Conditions

13.1 Musculoskeletal Symptoms

13.1.1 Clubbing

- Clubbing of the fingers and toes is the rule rather than the exception in children with CF by middle childhood.
- It is associated with the progression of suppurative lung disease, although the degree of clubbing may fluctuate.
- Stages of clubbing have been described as follows:[1]
    - **Stage 1:** Loss of angle between the nail bed and the cuticle.
    - **Stage 2:** Convex nails and an increase in the bulk of the terminal pulp.
    - **Stage 3:** Increase in the nail curvature and widening of the phalanges.

13.1.2 Overview of Joint Disease

- Joint disease affects approximately 12% of CF patients overall.[2]
- More common in adults, tending to occur from adolescence onwards.
- Presents as episodic arthritis and/or hypertrophic pulmonary osteoarthropathy (HPOA).

13.1.3 CF related Arthropathy

- Commonly presents as an asymmetric polyarthritis, involving mainly large joints (most commonly the knees[3]), although monoarthritis can also occur.
- May involve any joint, and the distribution of affected joints may differ with each episode.
- Joints are typically red, hot, tender and swollen.
- Episodes may last for days to a couple of weeks and resolve spontaneously, or longer term progress to persistent synovitis with frequent recurrences.
- Arthritis is usually non-erosive[4] and permanent disability is very rare.
- Joint aspiration commonly reveals sterile inflammatory changes[5] and biopsies have demonstrated non-specific synovitis.[6]

Management

- Non-steroidal anti-inflammatory drugs (NSAIDs)
    - Most patients can be managed with NSAIDs on an intermittent basis.
    - When using NSAIDs or aspirin consideration of important co-morbidity should be considered: These include:
        - Haemoptysis
        - Significant asthma
        - Synthetic liver dysfunction

- Intra-articular steroid injection. [Some patients may benefit for immediate control of synovitis.]
- Systemic steroids or immunomodulatory therapy such as methotrexate. [Rarely required.]
- Whilst data linking arthropathy to periods of pulmonary exacerbations exists[7] (suggesting an underlying reactive arthritis), it is inconsistent.
- Circulating immune complexes are found in the sera of patients with CF. [8]
    - May suggest a mechanism linking arthropathy to pulmonary exacerbations.[9]
- Patients with CF have been shown to have higher titres of rheumatoid factor than healthy controls and rheumatoid arthritis, spondyloarthropathy and sarcoidosis have been reported in CF but are unlikely to be related to the disease.
- Other complications such as mechanical back pain and patellofemoral syndrome have also been reported especially in older patients.[10]

13.1.4 HPOA

- Occurs in up to 7% of patients with CF.
- Has a later onset than arthritis, with a mean age of 20 years.[5]
- Likely to be related to underlying disease severity rather than acute exacerbations.[10]
- Several diagnostic criteria for HPOA have been proposed but there is no generalised agreement. Proposed criteria include:
    - Pain along the long bones with periostitis.[5]
    - Finger and toe clubbing with symmetric arthralgia and in some cases, effusions in the knees and/or ankles.[7]
- Most have symmetrical polyarthritis with pain and effusions in large joints (knees, wrists and ankles).
- X-ray changes of HPOA include:
    - *Acute* - periosteal reaction adjacent to the ends of long bone particularly at the wrists and ankles
    - *Chronic* - new bone formation in the mid-shaft of the long bones.
- Underlying aetiology of HPOA is unknown
- Fares may coincide with infectious pulmonary exacerbations.[11]
- Overall it is associated with a worse prognosis.[5]

Management:

- Improvement of respiratory function
- Analgesia, using anti-inflammatory medication
- Report of bisphosphonate utility in HPOA in CF.[12]

13.1.5 Ciprofloxacin related musculoskeletal manifestations

- Ciprofloxacin has been associated with acute inflammatory arthritis and tendonitis.
- Tendon rupture has been reported and may require surgical repair (MIMS).

13.2 Sinonasal disease

13.2.1 Background

- Symptomatic and asymptomatic sinonasal disease is very common in children with CF, and may contribute to their pulmonary status.
- Normal drainage of the paranasal sinuses involves interactions between both secretory and transport mechanisms. It is dependent on the:
    - Amount and composition of mucus produced
    - Ciliary clearance efficiency
    - Rate of mucus absorption
    - Patency of ostia that enable ventilation and passage for mucus clearance.
- CF predisposes the sinonasal mucosa to chronic inflammation and recurrent infection, by allowing mucus stasis to develop and reducing sinus aeration.
- Patients with CF have impaired mucociliary clearance, in spite of normal ciliary ultrastructure and ciliary beat frequency.
- The viscoelastic properties of the mucus contribute to the mechanical obstruction of the sinus ostia.
- The most common sinonasal pathogens encountered in the sinuses are *P. aeruginosa*, *H. influenzae*, and anaerobes.[13]
- *S. aureus* is rarely cultured.

13.2.2 Nasal polyps

- Reported incidence in CF varies from 6-48%.[14, 15]
- Seldom reported before the age of 5 years or after the age of 20 years.
- Affected children tend to have milder gastrointestinal and pulmonary symptoms.[16]
- Pathophysiology of polyps is unclear, with suggested explanations including:
    - Dilated mucous glands causing obstruction of the capillaries and local oedema.[17]
    - Chronic nasal mucosal inflammation.[18]
    - Atopy.
- Incidence of asthma or rhinitis among patients with nasal polyps has been reported as 39%.[15]
- Prevalence of atopy in patients with CF, however, is not higher than the general population.[19]
- Histopathology differs from that of allergic polyps[20] making allergy as an underlying aetiology unlikely.

13.2.3 Symptoms and Signs

Symptoms

- Sinonasal disease symptoms are commonly present but rarely reported voluntarily.
- Common symptoms include:
  - Nasal obstruction, and purulent rhinorrhea in younger children
  - Headaches in adolescents
- Others include:
  - Mouth breathing
  - Agitated or restless sleep
  - Activity limitation
  - Facial pain
  - Snoring
  - Voice change
  - Postnasal drainage with morning cough
  - Constant throat clearing
  - Anosmia

Physical examination signs

- Relate to chronic nasal obstruction and purulent nasal discharge.
- Anterior rhinoscopy: swollen erythematous nasal mucosa and/or polyps.
- Development of polyps:
  - Perennial rhinitis leads gradually to nasal obstruction, becomes persistent
  - Significant reduction in airflow can cause reduced sense of smell and flavour perception.
- Polyps
  - Usually multiple and bilateral.[15]
  - Usually arise from underneath the middle turbinate.
- Younger children are often mouth breathers with purulent discharge at the nares and in the posterior pharynx.
  - May also have a cobblestone appearance.
- Thickening of the bony walls of the ethmoid sinuses may lead to broadening of the nasal bridge in school age children.
  - In severe cases can cause proptosis.
- Tenderness on palpation of the sinuses is a rare finding.

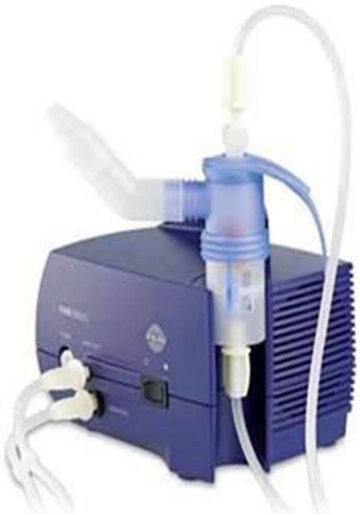
13.2.4 Investigation

- Investigation of choice for assessing the sinuses is CT scan.
- Conventional sinus radiographs are opacified almost universally after the age of 8 months.[21]

13.2.5 Treatment

- Medical management is the initial step in treating sinonasal disease in CF.
- Treatment options include:
    - Intranasal steroids
    - Nasal decongestants
    - Antihistamines
    - Saline irrigation
    - Nebulised or oral antibiotics
- Intranasal corticosteroids
    - Benefits of intra-nasal corticosteroid treatment of polyps in have been shown for the general population[22] but not to date for the CF population.[23]
    - Nasal ICS relieve obstructive symptoms, but are less effective at relieving rhinitis or sneezing. These include mometasone and budesonide intranasal spray.
    - Intranasal aerosol administration is preferred to oral, as systemic absorption is limited
    - Intra-nasal drops have not been shown to be more effective.
    - Nasal irrigation with a solution of budesonide in sodium chloride 0.9% has been used in severe disease
- Oral corticosteroids (OCS)
    - A short course of OCS can be used in those who do not respond to intra-nasal, presumably due to inadequate distribution due to blockage.
- Antihistamines or leukotriene receptor antagonists (e.g. montelukast)
    - May alleviate rhinitis symptoms if there is a clear history of seasonal allergies.
- Hypertonic saline
    - Helps to decongest nasal mucosa
    - Shown to decrease ciliary beat frequency[24] the benefit of the mucolytic effect is felt to outweigh this.
    - 3% hypertonic saline is the most commonly recommended strength.
    - CHW pharmacy stocks 6% hypertonic saline, but can make up lower strength concentrations as required.
        - Can also be given via Pari Sinus nebuliser for more targeted deposition.
- Nasal irrigation with a commercial sodium chloride and bicarbonate solution such as Sinus Rinse is another alternative.
- Antibiotics:
    - With sinusitis, empiric antibiotic therapy is recommended for 3-6 weeks.
    - Optimum duration of treatment is not known, but a long course is advocated due to impaired mucociliary function and mucus stasis.

- Choice of antibiotic therapy is empiric and based on the fact that similar pathogens are found in the upper airways and lungs[25] including *P. aeruginosa*.
- Nebulised delivery of anti-pseudomonal antibiotics has also been shown to be effective using the Pari Sinus nebuliser.
- Anecdotally, another CF centre has had beneficial experience using the following approach to treatment, administered with the Pari Sinus nebuliser has had good success at another centre eradicating sinus based *P. aeruginosa:*
  - 2mL nebulised budesonide (1mg/2mL)
  - And followed by 2mL of Tobramycin (IV formulation, 80mg/2mL)
  - Note: tobramycin and budesonide are physically incompatible so are given separately
  - Given twice daily, nebulised for as long as can tolerate (Total treatment time of approximately 15 mins)
  - Alternating nostril every few minutes during dose administration, applying resistance to the other nostril (e.g. loose tissue and finger)
  - Given for one month
  - Nasal rinse sample following treatment to assess success
- Transmaxillary aspiration is not routinely recommended.
- Frequent antibiotic courses for pulmonary exacerbations may explain why complications of sinusitis are uncommon in CF patients, despite the high incidence of sinusitis.



The Pari Sinus Nebuliser is designed to deliver medication directly to the sinuses via a pulsating aerosol.

Correct technique needs to be taught to the patient as it is a unique technique, requiring breath hold: Inhalation should be about 2.5 mins in each nostril.

The pump can also be used for inhalation to the lower respiratory tract by using the non-pulsating port.

- Pseudomonas infections are serious complications encountered in post transplanted patients, and the reservoir for these infections is thought to be the nasal sinuses.[26]
  - Some institutions to assess for sinonasal disease routinely, as part of their pre-transplant assessment, and use bilateral ethmoidectomy and maxillary antrostomy at the time of transplant in certain patients.
- Surgery should be considered when medical management has failed.

13.2.6 Outcome

- Intranasal steroids reduce polyp size but do not cure polyps.
- Severity varies from a single episode requiring intranasal steroids to lifelong disease requiring continuous medical therapy and surgical interventions.
- Long-term treatment with intra-nasal steroids does not affect growth in children.[27]
- Nasal polyps have a high recurrence rate post resection:
    - Reflects the wide spread inflammatory nature of the pathology, although mild disease may have a long-lasting effect.
    - In more severe disease, the recurrence rate ranges from 61-89%[14, 28] with over half having more than two polypectomies.
    - The recurrence rate is lower, 13-35%[14, 28] when combined with a more extensive procedure.

13.3 Salt Depletion

- Hypokalaemic, hypochloraemic metabolic alkalosis is a long recognised complication of CF. [29]
    - Has been attributed to impaired transport of chloride via a cAMP-regulated channel (the CFTR)
    - Leads to excessive sweat chloride and potassium losses, volume depletion, secondary hyperaldosteronism, and alkalosis-induced redistribution of potassium from extracellular to intracellular fluid.
- Infants and young children with CF living in warmer areas are most susceptible.
- Occasionally, older children and adults may present with multiple episodes of “sunstroke” before the diagnosis of CF is considered.
- However, all patients are prescribed added salt to their diet from diagnosis.
    - Typically, begins with ¼ teaspoon of table salt per day in infancy
    - Increases to about a teaspoon per day in the toddler years.
    - Salt is added to foods in the home.

13.4 Long Lines / Implanted Vascular Access Devices

13.4.1 Long Lines

- The venous access of choice for patients with CF who are admitted for treatment of a chest infection is an IV long line (also known as a Peripherally Inserted Central Catheter, or PICC line).
    - This is preferred to repeated peripheral IV lines due to the anticipated length of the antibiotic course (minimum two weeks).

- Long lines can be inserted either using:
  - Inhaled Nitrous Oxide for sedation on the ward or in theatre (usually for older adolescents) or
  - In theatre using general anaesthetic.
- In most cases anaesthetic staff insert the long lines although qualified Registrars and Fellows may insert them.
- IV long lines should be treated as central lines if the tip of the line is thought to enter the thorax.
- Patients with CF should be disconnected from their infusion, in between IV antibiotic doses, during the day, if appropriate, to encourage activity.

13.4.2 Implanted Venous Access Devices (IVAD)

- IVADs (often referred to as "ports") are considered for patients with CF who:
  - require frequent admission for intravenous antibiotics (usually twice or more per year)
  - for whom insertion of intravenous long lines has become difficult
  - who unable to maintain intravenous access with peripherally inserted lines for more than a few days
- IVADs are inserted surgically. Prior to insertion the patient and family should understand:
  - The purpose of a IVAD
  - How it is inserted
  - Where it is located
  - Long term care of device – including the need for monthly flushing.
- Options for positioning of IVADs include the groin, anterior chest wall, or arm.
- The anterior chest wall is the preferred site for IVAD insertion.
  - Patients may request groin placement due to the lack of visibility to peers, but recent experience has not been favourable, and infection risk remains a big concern.
  - Chest wall position should take into account possible interference of a chest wall device with chest physiotherapy (percussion).
- Arm ports (in the brachial area) are increasingly used in adult patients, but are not suitable in younger patients due to difficulty locating the IVAD once inserted due to increased subcutaneous fat.
- A guideline for care and management of IVAD's at home is available in the Home Care guidelines manual entitled: Care of Implanted Venous Access Devices at Home
- It is imperative that those accessing the IVAD follow aseptic technique to minimize infective complications.

13.5 Post procedural pain control in inpatients

13.5.1 Background

- Children with CF may require admission to hospital for IV antibiotics and intensive physiotherapy for acute exacerbations of their underlying lung disease.
- In patients with more advanced disease this may be on a regular basis to control symptoms of chronic pseudomonas colonisation (e.g. every 3 months).
- Additional procedures during the admission may include insertion of a peripheral long line or central line, or insertion of a port, if venous access is difficult or regular admissions are planned, and bronchoscopy and lavage.
- Post-procedure pain (e.g. following ports) can have a significant impact on recovery, impairing respiratory effort and clearance of airway secretions.
- Poor chest expansion and impaired coughing predisposes the child to segmental atelectasis and collapse, especially in those with suppurative lung disease.
- Pain also impacts on co-operation with physiotherapy.
- Good analgesia can help facilitate aggressive physiotherapy and post-operative recovery.
- Adequate analgesia will also help prevent secondary scoliosis and aids mobilisation.

13.5.2 Recommendations

- Patients admitted for port insertion should be referred to the pain team, ideally notifying pre-operatively to facilitate prompt post-operative analgesia.
- Following insertion of a port, Patient/Nurse Controlled Analgesia (PCA/NCA) should be prescribed (initially without a bolus).
- Daily review should occur to assess the need for the PCA/NCA.
- Regular administration of paracetamol and a NSAID for 48 hours should also be encouraged.
    - Use of paracetamol and an NSAID can reduce opioid requirements.
    - Caution should be used with NSAIDs in CF patients with co-existing asthma, and with paracetamol in those CF patients with liver disease.

13.5.3 Respiratory Failure

- Extreme caution should be exercised if prescribing opioids to children with severe respiratory compromise.
- Pain, sedation levels and pulse oximetry need to be closely monitored.
- CO_2 retention may be an issue in those children with established lung disease or severe upper airway obstruction.
- Analgesia using paracetamol and non-steroidal anti-inflammatory drugs should be maximised.
- Initial doses and dose titration should be conservative.

13.6 Exercise testing

- Exercise testing is a valuable tool for gauging the global impact of CF.
- Exercise testing provides a dynamic assessment of lung function and therefore may detect subtle deficits.
- Exercise tolerance reduces as the patient's lung function deteriorates and there is a high correlation between exercise tolerance measured by aerobic fitness and long term survival.
- Exercise tolerance has become an important outcome measure in interventional trials in patients with CF.
- The "gold standard" assessment of exercise tolerance is measured in the laboratory using treadmills or cycle ergometer and gas analysis.
- This highly specialised equipment is available in the RFU laboratory at The Children's Hospital, Westmead.
- Alternatively, a variety of "field" tests such as the shuttle walk or shuttle runs may be used to estimate the child's fitness.
- Several of these field tests have now been validated.[30]
- All children with CF over the age of 6 years perform a formal exercise test annually in our clinic.

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14 Research

14.1 Background

- Research is an integral component of health care.
- The results of research studies provide information pertaining to:
  - The incidence of disease
  - The optimal use of existing therapies
  - A greater understanding of the causes and course of a disease
  - The utility of new therapies.
  - CHW is committed to excellence in research and the value of this research to enhancing the health and lives of children with CF.

14.2 Aim

- To perform research which is relevant to the health and well-being of patients with CF and which is ethical, accurate and of international quality.

14.3 New Research Projects

- All research projects must be presented to the entire CF team before submitting an application for ethical approval of the project.
- Presentations can be made in one of three forums:
  - At the dedicated Respiratory Research meetings – 1st and 3rd Mondays each month (8:30-9:30am),
  - At the weekly CF Team business meeting – held on Tuesdays at 11-12:30am.

    Investigators should inform the Clinic Coordinator that they wish to present at a meeting so the presentation can be included in the agenda.
  - At a designated research journal clubs – held every three months on a Thursday morning 9-10am.
- Closing dates for Ethics Committee submissions are usually in January, March, May, June, August, September and November, the exacts dates being available from the Research Office: see http://intranet.schn.health.nsw.gov.au/research/human-research-ethics

14.4 Authorship of research output from the CF Unit at CHW

- In accordance with the submission policies of many medical and scientific journals, the minimum requirement for authorship should accord with the 'Vancouver Protocol'. Thus, authorship is substantial participation, where all of the following conditions are met:
  - Conception and design, or analysis and interpretation of data; and
  - Drafting the article or revising it critically for important intellectual content; and
  - Final approval of the version to be published.

- Participation solely in the acquisition of funding or the collection of data does not justify authorship.
- General supervision of the research group is not sufficient for authorship.
- An author's role in a research output must be sufficient for that person to take public responsibility for at least that part of the output in that person's area of expertise.
- No person who is an author, consistent with this definition, must be excluded as an author without their permission in writing.
- Authorship of a research output is a matter that should be discussed between researchers at an early stage in a research project, and reviewed whenever there are changes in participation.
- When there is more than one co-author of a research output, one co-author (by agreement amongst the authors) should be nominated as executive author for the whole research output, and should take responsibility for record-keeping regarding the research output.
- Where the research is published, including electronically, all co-authors of a publication must acknowledge their authorship in writing in terms of, at least, the minimum acceptable definition.
- This signed statement of authorship must specify that the signatories are the only authors according to this definition.
- It must state that the signatories have seen the version of the paper submitted for publication.
- If, for any reason, one or more co-authors are unavailable or otherwise unable to sign the statement of authorship, the Head of their Department may sign on their behalf, noting the reason for their unavailability.
- The authors must ensure that others who have contributed to the work, but who are not authors, are recognised in the research output.
- Therefore, the fact that the work is a collaborative effort of the entire team should be acknowledged either by naming all team members for short term-projects or the departments involved for longer term projects.
- The appropriate form of acknowledgment is at the discretion of the authors and may be dependent upon the journal to which the manuscript is being submitted.

14.5 Review of Manuscripts prior to submission for publication

- A manuscript is not to be submitted until 7 days after tabling one complete copy of the draft at an appropriate research meeting and circulation by email to all team members the same day.
- Any team member who wishes to make comments, must communicate them directly to the relevant author within the following 7 days.

14.6 Register of Research projects

- A register is to be kept of the status of all research projects pertaining to CF.
- The Register is to be in the form of collation of the appended Registration of CF Research Project Forms.
- The Register is to be retained by the Clinic Coordinator.
- One copy of all research output published by members of the CF team which relate to CF research carried out by or in conjunction with the CF Unit at CHW is to be placed in the Research register.
- A written acknowledgment of authorship, must be deposited in the Register, at the time of submission of the research output for publication.
- This policy applies to all forms of research output including abstracts submitted for presentation at meetings.

14.7 Dissemination of Research Results to Research participants

- The onus is on all investigators to individually feedback (in writing in educated layman's terms) the results of a research study to the participants and their parents at the conclusion of a research study.
- Results should also be disseminated via the CF Newsletter which is produced by the Clinic Co-ordinator and where possible, at parent information evenings.

14.8 Resources

14.8.1 Ethical Conduct of Research

- National Statement on Ethical Conduct in Research Involving Humans (1999) - outlines the acceptable ethical standards for human research as formulated by the National Health and Medical Research Council.
- It is available for the following website which contains useful information for those undertaking human subject research: http://www.nhmrc.gov.au/ethics/human/conduct/index.htm

14.8.2 Ethical Approval

- Human Research Ethics Committee Submission Guidelines provides details in regard to application for ethical approval of research projects is available under "Ethics" in the Resources submenu of the following website: http://chw.schn.health.nsw.gov.au/ou/research/

15 Cystic Fibrosis Pharmacopoeia

This pharmacopoeia is a dosing guide for many of the medications commonly used in the management of cystic fibrosis. However, it is not exhaustive and consultation of other references may be required. Neonatal dosing and dosage adjustment for renal or hepatic dysfunction are beyond the scope of this document and specialist references should be utilised. For post-transplant medication regimens, refer to the Lung Transplant protocol of the relevant transplant unit.

For **anti-depressant medications** used in adolescents, see Table 7.1. For combined **oral contraceptive pills** (OCPs) used in adolescents, see Table 8.2.

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Acetylcysteine (NAC)	PO	Meconium ileus Neonates: 200-400mg/dose DIOS 1 month-2 years: 0.4-3g 2-7 years: 2-3g >7 years: 4-6g	Meconium Ileus 400mg DIOS 1month- 7years: 3g Greater than 7yrs:6g	For MI, dose may be given up to 3 times a day For DIOS, dose is given once only	Ampoule for IV use 200mg/mL	Use injection orally. Filter the dose drawn from the ampoule and dilute to a concentration of 50mg/mL. To mask highly unpleasant taste, use fruit juice or soft drink as diluent. In neonates, administer via nasogastric tube.	
Amikacin	IV	<10years: 30mg/kg/dose ≥10 years: 24mg/kg/dose	1.5g/dose	DAILY	Vial for IV use 500mg/2mL (IV preparation suitable for nebulising)	ID approval required Trough levels currently used to monitor. Aim: Trough <4mg/L Contact antimicrobial stewardship pharmacist for AUC monitoring	
	Neb	6-12 years: 250mg/dose >12 years: 500mg/dose	6-12years: 250mg/dose >12 years: 500mg/dose	BD		ID approval required Dilute to 4mL with 0.9% sodium chloride May cause bronchospasm in susceptible patients – tolerance test recommended.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Amoxycillin	PO	15-30mg/kg/dose	1g/dose	TDS	Capsule 250mg Capsule 500mg Suspension 250mg/5mL		
Amoxycillin-Clavulanic Acid "Augmentin Duo"	PO	22.5mg/kg/dose (Dose based on amoxycillin component)	875mg amoxycillin/ dose (equal to 125mg clavulanic acid)	BD	Tablet 500mg/125mg Tablet 875mg/125mg Suspension 400mg/57mg/5mL	May cause liver dysfunction in pre-existing liver disease	4.4.1
Amphotericin (Conventional) "Fungizone®"	Neb	<10 years: 5mg/dose >10 years: 10mg/dose	<10 years: 5mg/dose >10 years: 10mg/dose	BD	Vial for IV use 50mg (IV preparation suitable for nebulising)	ID approval required Not registered in Australia – completion of Special Access Scheme form required, Category A. May cause bronchospasm in susceptible patients – tolerance test recommended. To prepare: Reconstitute with 10mL WFI = 5mg/mL. Further dilute to 3mL with WFI. Do NOT dilute with sodium chloride. Liposomal amphotericin may be used if poor tolerance to Fungizone. A specialised nebuliser is required (Halolite or Pro-Dose AAD systems). Contact ID and pharmacy regarding dosing and preparation of solution.	4.7.3

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Amphotericin Liposomal "Ambisome®"	IV	Starting dose is 1mg/kg/dose then increase on Day 2 by 1mg/kg/dose up to 3mg/kg/dose (Higher doses may be used in consultation with ID)	5mg/kg/day	DAILY	Vial for IV use 50mg	ID approval required Check renal/liver function and EUCs 3 times per week. Caution with other nephrotoxic drugs.	
Atenolol	PO	12.5mg/dose Evidence for efficacy available for adolescents and above. For younger children consider smaller starting dosing	50mg/dose	DAILY	Tablet 50mg Oral solution 5mg/mL	Grade up until haemoptysis settles Use with caution in concomitant asthma	
Azithromycin (Antimicrobial dosing)	PO	10mg/kg/dose	500mg/dose	DAILY	Tablet 500mg Suspension 200mg/5mL	ID approval required.	4.4.6
Azithromycin *(Anti-inflammatory dosing)*	PO	≥ 6 years old and ≥25kg and <40kg: 250mg/dose ≥40kg: 500mg/dose	500mg/dose	Once a day for 3 days a week		ID approval required Treatment should be reviewed after 12 months. Consider treatment breaks of 6-12 months duration.	4.5.5

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Aztreonam	IV	50mg/kg/dose (see total daily dosing and frequency)	200mg/kg/day OR 8g/day	TDS or QID	Vial for IV use 1g (IV preparation suitable for nebulising)	ID approval required	
	Neb	500mg-1g/dose *This dose reflects experience but is not supported in available literature*	1g	BD		ID approval required May cause bronchospasm in susceptible patients – tolerance test recommended. Use only when organism develops clinical or microbiological resistance to other inhaled antibiotics.	
Aztreonam Lysinate "Cayston®"	Neb	≥7 years: 75mg/dose	75mg	TDS (Do not administer doses less than 4 hours apart)	Vial for nebulisation 75mg	ID approval required. Patient must meet criteria for supply – contact pharmacy for details of eligibility criteria. To be used for 28 days, followed by 28 days off. May cause bronchospasm in susceptible patients – tolerance test recommended. Use only when organism develops clinical or microbiological resistance to other inhaled antibiotics.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Budesonide	Intra-nasal	**Maintenance:** > 6 years-12years: 32microg/dose each nostril >12 years: 64microg/dose each nostril **Exacerbation:** > 6 years-12years: 32microg/dose each nostril > 12 years: 64microg/dose per nostril	32microg/day (per nostril) 64microg/day Per nostril	DAILY BD	Nasal spray "Rhinocort" 64microg/spray 32microg/spray (Not kept at CHW)	Taper dose when symptoms controlled. 32microgram spray is available without prescription at community pharmacies.	
	Nasal irrig-ation	Adolescents and older: 500microg in 240mL sodium chloride 0.9% (using Sinus Rinse bottle) and 120mL instilled into each nostril	250microg/ nostril	DAILY	Respules "Pulmicort" 500mcg/2mL		

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Calcium Salts	PO	Age RDI 1-3 years: 500 mg/day 4-8 years: 700 mg/day 9-11 years: 1,000 mg/day 12-18 years: 1,300 mg/day Dose should be calculated by subtracting dietary intake from RDI Consult dietician.		Given in 2 divided doses.	"Caltrate" Tablet: Elemental calcium 600mg (as 1500mg calcium carbonate) "Caltrate with D" Tablet: Elemental calcium 600mg (as 1500mg calcium carbonate) and colecalciferol 500 units "Caltrate Plus" Tablet: Elemental calcium 600mg (as 1500mg calcium carbonate) and colecalciferol 400 units (refer to Product information for mineral contents) "CalSource" Effervescent Tablet: Elemental calcium 1000mg (as mix of lactate, gluconate and carbonate salts) "Cal-Sup" Chewable Tablet: Elemental calcium 500mg (as 1250mg calcium carbonate) Oral Suspension: Elemental calcium 40mg/mL (as 100mg/mL calcium carbonate)	100mg elemental calcium = 2.5mmol calcium	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Caspofungin	IV	≥ 3months: 70mg/m^2/dose on Day 1, then 50mg/m^2/dose on Day 2 onwards	70mg/dose	DAILY	Vial for IV use 50mg or 70mg	ID approval required Reduce dose in liver impairment. Refer to CHW Caspofungin Drug Protocol:	
Cefepime	IV	50mg/kg/dose	2g/dose	TDS	Vial for IV use 1g	ID approval required	
Cefotaxime	IV	50mg/kg/dose	2g/dose	TDS or QID	Vial for IV use 500mg, 1g or 2g (Availability of strengths may vary)	ID approval required	
Ceftazidime	IV	50mg/kg/dose	2g/dose	TDS	Vial for IV use 1g or 2g (IV preparation suitable for nebulising)	ID approval required	
	Neb	1g/dose	1g	BD		ID approval required Used for treatment of Burkholderia cepacia. May cause bronchospasm in susceptible patients – tolerance test recommended. Compliance may be poor due to unpleasant taste. BNFC- recommends 1g nebulised for chn 1month - 18years	4.4.5

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Cephalexin	PO	15-25mg/kg/dose	1g/dose	QID	Capsule 250mg Capsule 500mg Suspension 250mg/5mL		
Ciprofloxacin	IV	10mg/kg/dose 15mg/kg/dose may be considered with input from ID Team.	400mg/dose	TDS	Bag for IV use 100mg/50mL or 200mg/100mL	ID approval required IV route only necessary when oral administration not possible as well absorbed when given orally Can cause arthropathy or tendonitis.	
	PO	15-20mg/kg/dose (20mg/kg/dose may be used in severe cases)	750mg/dose	BD	Tablet 250mg Tablet 500mg Tablet 750mg	ID approval required Milk reduces absorption – avoid milk for at least 30 minutes pre and post dose Sun protection required. Can cause arthropathy or tendonitis.	4.2.1 4.4.4 13.1.5
Clarithromycin	PO	7.5mg/kg/dose (15mg/kg/dose for treatment of Mycobacteria)	500mg/dose (1g/dose for Mycobacteria)	BD	Tablet 250mg Tablet 500mg Suspension 250mg/5mL	ID approval required Can cause tooth and tongue discolouration May be used in the treatment of NTM/MAC	
Clindamycin	PO	10-15mg/kg/dose	600mg/dose	TDS	Capsule 150mg	Capsules may be opened and dispersed; the resulting solution is very bitter. Mask with honey or chocolate yoghurt	4.4.3

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Colistimethate sodium [Colistin/ Colomycin] "Tadim®"	Neb	1-2 million units/dose (1 million units is referred to as 1 mega unit by some sources) *Reduced doses (0.5 – 1 million units/dose) have been used for children less than 2 years old (BNFC)*	2 million units/dose	BD	Vial for nebulisation 1 million units 1 million units = 33.33mg colistin=80mg colistimethate sodium	Do not mix with tobramycin. May cause bronchospasm in susceptible patients – tolerance test recommended; may improve with further dilution using sodium chloride. Monitor renal function	
Colistin (as colistemethate sodium)	IV	1.6mg/kg/dose of colistin (= 5mg/kg/day)	66.6mg/dose of colistin	TDS	Vial for IV use 150mg/2mL (1mg of colistin = 30000units)	ID approval required Dose should be prescribed according to Colistin base Check other dosing references carefully as some sources use mg of colistemethate sodium or units Monitor renal function	
Dornase Alpha "Pulmozyme®"	Neb	2.5mg/dose	2.5mg/dose	DAILY	Nebule 2.5mg/2.5mL	Do not dilute contents of nebule or mix with other drugs.	4.8.1
Doxycycline	PO	4mg/kg/**day** on Day 1 in two divided doses then 2mg/kg/**day** in one or two divided doses	100mg/dose	BD on Day 1 then OD or BD there-after	Tablet 50mg Tablet 100mg	Avoid in <12 years as can discolour teeth and bone. Take with meal/glass of milk or water to avoid oesophageal irritation and remain upright for an hour after the dose. Risk of photosensitivity.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Erythromycin *Note: Available as erythromycin base (capsule only) or ethyl succinate salt [EES] (liquid or tablet)*	PO	10mg/kg/dose (EES) For children ≥40kg only: 250mg (base) is equivalent to 400mg (EES)	EES: 400mg/dose Base: 250mg/dose	QID	EES: Tablet 400mg Suspension 200mg/5mL Base: Capsule 250mg	Recommended to be given QID, but can also be given TDS. If giving TDS, use 15mg/kg/dose. Risk of pyloric stenosis in neonates	
Esomeprazole *"Nexium®"*	PO	3–5 kg: 2.5 mg 5–7.5 kg: 5 mg 7.5-20 kg: 10 mg >20kg: 10-20mg	20mg/day (May be increased to 20mg BD in refractory cases)	DAILY	Sachet of granules for oral suspension 10mg	Restricted to patients requiring administration via enteral feeding tube or infants <10kg (where calculated omeprazole dose would be <10mg). All other patients should receive omeprazole tablets (either swallowed whole or dispersed in water). Do not use esomeprazole in neonates.	
Ethambutol	PO	15mg/kg/dose (Higher doses have been used in consultation with ID)	1.5g/dose	DAILY	Tablet 100mg Tablet 400mg	For treatment of NTM/MAC Can cause optic neuritis and requires visual acuity checks Not recommended in children <6 years of age due to difficulty in eye assessment.	4.4.6
Flucloxacillin **(Treatment dosing)**	IV	25-50mg/kg/dose	2g/dose	QID (may be given q4h in severe infection)	Vial for IV use 500mg Vial for IV use 1g		
	PO	25-50mg/kg/dose	1g/dose	QID	Capsule 250mg Capsule 500mg Suspension 250mg/5mL	Take one hour before food or two hours after food. *QID dosing is preferred; however, for compliance TDS dosing has been used historically.	4.4.2

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Flucloxacillin (Prophylaxis dosing)	PO	15mg/kg/dose	500mg/dose	TDS or QID	Suspension 250mg/5mL	For infants <1 year old Take one hour before food or two hours after food. *QID dosing is preferred; however, for compliance TDS dosing is acceptable.	3.2 Table 3.1
Fusidate Sodium	PO	12mg/kg/dose Suggested rounding: - 5-12years: 250mg/dose - greater than 12years: 500mg/dose	500mg/dose	TDS	Tablet 250mg	ID approval required. If possible, round dose to 250mg or 500mg. May be crushed and mixed with chocolate yoghurt or sauce due to poor palatability. Restricted to use in combination with another antibiotic for treatment of proven serious staphylococcal infections	4.4.3
Gentamicin	IV	10mg/kg/dose **(then as guided by levels)**	600mg/day **(then as guided by levels)**	DAILY	Ampoule for IV use 80mg/2mL (IV preparation suitable for nebulising)	Dose is usually given at 0630 to allow for samples at 2 and 6 hours post for AUC calculation (Aim 90-110mg.h/L)	
	Neb	<10 years: 80mg/dose ≥10 years: 160mg/dose	160mg/dose	BD		Further dilute to a minimum of 4mL Tobramycin is usually used first line in CF patients; gentamicin is typically used for non-CF bronchiectasis May cause bronchospasm in susceptible patients – tolerance test recommended.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Imipenem-Cilastatin	IV	25mg/kg/dose (of imipenem)	1g/dose	QID	Vial for IV use 500mg (contains 500mg cilastatin)	ID approval required	
Ibuprofen	PO	As analgesic and/or antipyretic: 5-10mg/kg/dose	40mg/kg/day **OR** Total 1600mg/day	3-4 times daily	Tablet 200mg Mixture 20mg/mL	For short term use only Use with caution in patient with history of haemoptysis, asthma and liver or kidney dysfunction.	
Itraconazole	PO	5mg/kg/dose **(then as guided by levels)**	200mg/dose **(then as guided by levels)**	BD	Capsule 100mg Liquid 10mg/mL	ID approval required Give capsules with food or an acidic drink (e.g. Coke or Orange Juice). Give liquid on an empty stomach 30 minutes before or two hours after food. Take first trough ≥7 days after commencing then monitor trough levels monthly (Aim 500-1000 microgram/L) Consider TDS dosing if sub-therapeutic levels persist. Watch signs of clinical toxicity – hepatotoxicity, tingling of hands or feet, headaches.	4.7
Lactulose	PO	Usual dose for constipation: 1mL/kg/day Usual dose for DIOS: 1mL/kg/dose	60mL/day Or 2mL/kg/day	Daily for constipation Or BD for DIOS	Oral liquid 3.34g/5mL	Nausea can be reduced by administration with water, fruit juice or meals.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Linezolid	IV	<12 yrs: 10mg/kg/dose **TDS** >12 yrs: 600mg/dose **BD**	1200mg/day	Age dependent	Bag for IV infusion 600mg/300mL	ID approval required. Reserved for resistant *S. aureus* where patients have not responded to conventional agents. Well absorbed orally - IV route only necessary when oral administration not possible. Monitor FBC weekly. Risk of ophthalmic neuropathy – requires eye exam before starting course and regularly if required for more than 28 days.	
	PO	<12 yrs: 10mg/kg/dose **TDS** >12 yrs: 600mg/dose **BD**	1200mg/day	Age dependent	Tablet 600mg Liquid 20mg/mL		
Macrogol with electrolytes "Movicol" and "Movicol-Half" Macrogol 3350 "ClearLax"	PO	- Children 2-5years: Use Movicol HALF – ONE sachet/day - Children 6-11years: Use Movicol HALF – TWO sachets/day - ≥12yrs: Use Movicol ONE sachet/day	- *Children 2-5 years:* Use Movicol HALF – ONE sachet/day - *Children 6-11 years:* Use Movicol HALF – FOUR sachets/day - *≥12yrs*: Use Movicol THREE sachets/day	Daily or in two divided doses	Sachets (polyethylene glycol 3350/sodium bicarbonate/sodium chloride/potassium chloride)	Contains 50.2mg potassium/sachet (Movicol) and 23.3g (Movicol-Half) Doses are for constipation For faecal impaction refer to product information Disperse the contents of one sachet of Movicol HALF in 62mL of water. Disperse the contents of Movicol in 125mL of water.	
Macrogol with electrolytes "Glyco-prep C" "ColonLYTELY"	Enteral tube	30mL/kg/hr (NG tube)	4L/day Or 120mL/kg/day	For 4-8 hours	Sachet of powder for oral solution 70g Each sachet makes 1L of solution	Volume and rate often based on tolerability. Repeat daily over several days until effluent clear. Solid food should be avoided for 2 hours prior to administration Not to be used in bowel obstruction or ileus.	

						Discontinue oral laxatives whilst using Glyco-prep C.	
Name	**Route**	**Usual Dose**	**Max Dose**	**Frequency**	**Preparations**	**Comments**	**Reference**
Meropenem	IV	40mg/kg/dose	2g/dose	TDS	Vial for IV use 1g Vial for IV use 500mg (IV preparation suitable for nebulising)	ID approval required To prepare for nebulisation: Reconstitute 500mg vial with 10mL. Store vial in fridge for 2nd dose within 24 hours May cause bronchospasm in susceptible patients – tolerance test recommended.	
	Neb	6-12 years: 125mg/dose >12 years: 250mg/dose	250mg/dose	BD			
Methyl-prednisolone	IV	10mg/kg/day This dose is for ABPA only	1g	Daily for 3 consecutive days each month for 6 months	Injection 40mg Injection 125mg Injection 500mg	Daily oral corticosteroids ceased whilst on pulsed therapy. See ABPA protocol When adequate control achieved increase interval between pulses. Lower rate of side effects compared to daily oral corticosteroid therapy. See Methylprednisolone (IV) – High Dose: Administration Drug Protocol for more information.	
Metronidazole	PO	7.5mg/kg/dose	400mg/dose	TDS	Tablet 200mg Tablet 400mg (not kept at CHW) Suspension 200mg/5mL	Give mixture on empty stomach. Give tablets with food Refer to CHW drug dosage guidelines for dosing for amoebiasis and giardiasis	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Minocycline	PO	>12 yrs: 100mg/dose	100mg/dose	BD	Tablet 100mg	May be used for treatment of *S. maltophilia.* Avoid in <12 years as can discolour teeth and bone. Take with meal/glass of milk or water to avoid oesophageal irritation and remain upright for an hour after the dose. Risk of photosensitivity.	
Mometasone	Intra-nasal	2-11years: 50mcg/dose (1 spray) each nostril 12 years & older: 100mcg/dose (2 sprays) each nostril	50mcg/day (per nostril) 200mcg/day (per nostril)	Usually ONCE a day but can be increased to BD for short periods	Nasal spray "Nasonex" 50mcg/spray	Taper dose when symptoms controlled.	
Multivitamin "Bio-Logical A and E"	PO	<12months: 0.5mL >12months: 0.5-1mL		DAILY	Bio-Logical A and E 1mL contains 2210 IU vitamin A and 102 IU vitamin E	If child takes Pentavite,or Vitabdeck, continue while supplementing for vitamin A & vitamin E.	
Multivitamin "Bio-Logical A,D and E"	PO	0-12 months: 0.7mL 1-3 years: 1mL 4-7 years: 1.5mL 8-18 years: 2mL	2mL/dose	DAILY	Solution: Vitamin A 2210IU/mL Vitamin D 1000 IU/mL Vitamin E 102 IU/mL		

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Multivitamin 'Centrum Kids"	PO	1 tablet for children greater than 3 years	1 tablet	DAILY	Centrum Kids contains Vitamin A 1500IU Vitamin D 100IU Vitamin E 10units	Used when cannot swallow VitaABDEK	
Multivitamins "Pentavite Infant Oral Drops "	PO	<12 months: 0.45mL 1-3 years: 0.9mL		DAILY	For composition of Multivitamin preparations see Table 6.5		
Multivitamins "VitABDECK"	PO	4-10 years: ONE capsule/dose >10 years: ONE - TWO capsules/dose	TWO capsules/ day	DAILY	For composition of Multivitamin preparations see Table 6.5		
Mupirocin 2% (Bactroban)	TOP	Apply twice a day to each nostril for 5 days		BD		For staphylococcal decolonisation	
Omalizumab See ABPA protocol Off label use with drug committee approval	SC	150mg or 300mg According to weight and IgE levels	375mg/dose	1-2 times per month	Injection 150mg	Requires Drug Committee Approval and Immunology consultation. Dose, frequency and duration as guided by Immunology Please refer to product information for details regarding dosing and administration	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Omeprazole	PO	0.5-1mg/kg/day	20mg/dose	DAILY	Tablet (dispersible) 10mg Tablet (dispersible) 20mg Oral suspension 2mg/mL	Oral suspension at CHW is restricted to neonates but can also be purchased from compounding pharmacies. For children with doses <10mg or with enteral tubes, consider esomeprazole sachets.	
Paraffin liquid (emulsified)	PO	12months-6years: Initially 10-15mL 7-12yrs:initially 20mL >12yrs: initially 40mL Dose may be increased or decreased by 5mL increments according to effect.		Daily or in divided doses	Liquid 200mL	These doses are for constipation Dose should aim to produce 1 soft motion with no oil leakage. Admin greater than or equal to 2 hrs before lying down Monitor for malabsorption of fat soluble vitamins	5.4.3
Paraffin liquid 100% (NOT emulsified)	PO	3-5yrs (martindale): 2.5-5mL 5-11yrs: 5-15mL >12yrs:15-45mL	As per dose column	Daily or in divided doses	Liquid 200mL	These doses are for constipation Dose should aim to produce 1 soft motion with no oil leakage. Admin greater than or equal to 2 hrs before lying down Monitor for malabsorption of fat soluble vitamins.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Pancreatic Extract (Pancreatic Enzyme Replacement) "Creon" and "Creon Micro"	PO	Doses based on lipase component: 5,000 units/kg/day For infants: 1 scoop Creon Micro per approx. 3-5g fat For children: 1 -2 Creon 10,000 capsule per approx. 8-10g fat	10,000units/kg/day or 4000units/ gram of fat /day	To be given with meals and half the dose with snacks	Enteric Coated Granules 60.12mg/100mg (Equivalent to 5000 units per scoop) Capsule 10,000 units Capsule 25,000 units	Dose based on 3 meals and 3 snacks per day	6.5.3 6.4
Piperacillin-Tazobactam "Tazocin®"	IV	100-150mg/kg/dose (as piperacillin) 1-6months 75mg/kg/dose	16g/day (based on piperacillin component)	QID	Vial for IV use 4g (contains 500mg tazobactam)		
Prednisolone	PO	1-2mg/kg/day Dose depends on indication)	60mg	DAILY	Tablet 5mg Tablet 25mg		
Ranitidine	PO	2-4mg/kg/dose	300mg/day	BD	Tablet (effervescent) 150mg Tablet 150mg Oral liquid 15mg/mL	Effervescent tablets can be dissolved in water, fruit juice and carbonated drinks (minimum volume 15mL).	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Rifampicin	PO	10mg/kg/dose	600mg/dose	DAILY	Capsule 150mg Capsule 300mg Suspension 100mg/5mL	Give dose one hour before or two hours after food. Can discolour urine, tears and other body fluids. May permanently damage soft contact lenses. May interact with other medications. Induces liver enzymes.	4.4.3 4.4.6
Roxithromycin	PO	2.5 - 4mg/kg/dose OR 6-11kg: 25mg/dose 12-23kg: 50mg/dose 24-40kg: 100mg/dose >40kg: 150mg/dose	150mg/dose (Also may be given as 300mg daily for patients >40kg)	BD	Tablet 50mg (dispersible) Tablet 150mg Tablet 300mg (not kept at CHW)	Give doses one hour before or two hours after food. Dispersible tablets require only a small amount of water (approximately 1 teaspoon) to form a suspension.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Sodium chloride (Toppin Tablets)	PO	All ages greater than 2years old: 1-3 tablets Toppin		1-3 divided doses	Tablet 600mg sodium chloride (=10.3mmol)	For children less than 2 years salt may be added to feed. Consult dietician. For older children, consider dietary sources of salt. Consult dietician. **Salt vs. Sodium:** List of conversions for salt and sodium: • 1 mmol sodium = 23 mg sodium • 1 g sodium = 43.5 mmol sodium • 1 g salt (sodium chloride) = 390 mg sodium • 1 tsp salt = 6 g salt ≈ 2,400 mg sodium = 104 mmol sodium = 104 mEq sodium To convert mmol to mg of sodium, chloride, or sodium chloride, multiply mmol by 23, 35.5, or 58.5 (the molecular weights of sodium, chloride, and sodium chloride), respectively. Therefore. 1/2 teaspoon = 1200mg sodium = 52 mmol 1/4 teaspoon = 600mg sodium = 26 mmol	
Sodium Chloride 6% [Hypertonic Saline] "HyperSal 6%"	Neb	4mL of either 3% or 6% solution. For 3% solution: Dilute with equal volume of water for injection (i.e 2mL WFI + 2mL HyperSal 6% for volume of 4mL)	4mL/dose	BD	Sachet of 6% Nebulising Solution 10mL	Dose usually given pre-physio. Alternatively give during physio with combined PEP device May cause bronchospasm in susceptible patients – tolerance test recommended. Salbutamol should be given in patients who experience broncho-constriction or where tolerance test is not feasible.	

						For sinus nebulisation, use 4mL of 3% solution via a Pari Sinus Nebuliser.	
Name	**Route**	**Usual Dose**	**Max Dose**	**Frequency**	**Preparations**	**Comments**	**Reference**
Sodium bicarbonate and Sodium Chloride Isotonic Sinus Rinse 'Sinus Rinse, Paediatric Kit'	Intra-nasal	For children 4 years and greater Use as directed.	BD	BD		Prepare as directed Provide patient instruction for preparation and administration Mix contents of one sachet in 120 mL lukewarm distilled water; use Pediatric Sinus Rinse squeeze bottle to squirt into nasal passage	
Sulfamethoxazole/ Trimethoprim [Cotrimoxazole] "Bactrim®, Septrin ®"	PO	4mg/kg/dose (Based on trimethoprim dose)	160mg/dose	BD (TDS for *S. maltophilia*)	Tablet 400mg/80mg Tablet 800mg/160mg Suspension 200mg/40mg/5mL	May be used for treatment of *B.cepacia* or *S. maltophilia*. Stop treatment if blood disorders such as decreased WCC or rashes develop (Stevens Johnson Syndrome) Advise patients to report all rashes, sore throats and fevers. Refer to specialist protocols for post-transplant prophylaxis.	
Teicoplanin	IV	10mg/kg/dose	400mg/ dose	12 hourly for first 3 doses then DAILY	Vial for IV use 400mg	ID approval required. Monitor renal function	
Ticarcillin Sodium - Potassium Clavulanate "Timentin®"	IV	100-150mg/kg/dose (as ticarcillin)	24g/day	QID	Vial for IV use 3g (Contains 100mg potassium clavulanate)		

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Tigecycline	IV	>8 years and up to 11 years: 1mg/kg/dose 12-17years: 50mg/dose Adult: 100mg/dose – loading dose then 50mg/dose.	50mg/dose (100mg/dose is loading dose in adults only)	12 hourly	50mg vial	Reserved for treatment of NTM. ID approval required. Infuse over 30-60 minutes. Nausea/vomiting a problem – prescribe regular oral ondansetron concurrently. In children less than 8 years consult ID	
Tobramycin	IV	10mg/kg/dose **(then as guided by levels)**	600mg **(then as guided by levels)**	DAILY	Vial for IV use 80mg/2mL	Dose is usually given at 0630 to allow for samples at 2 and 6 hours post for AUC calculation (Aim 90-110mg.h/L)	
Tobramycin "TOBI®"	Neb	>6 years: 300mg/dose	300mg/dose	BD	Ampoule for nebulization 300mg/5mL	May cause bronchospasm in susceptible patients – tolerance test recommended. When used for colonisation (see section 4.4.4) administer doses for one month on and one month off. PBS Section 85 - Not available through Hospitals (except for test dose)	4.4.3 4.4.4 13.2.5
Tobramycin "Tobra-Day®" Preservative free	Neb	<10yr: 80-125mg/dose ≥10yr: 160-250mg/dose	250mg/dose	BD	Vial for nebulization 500mg/5mL Store remainder of vial in fridge for second dose.	May cause bronchospasm in susceptible patients – tolerance test recommended. The IV injection has previously been used for nebulisation but as current product contains preservative, it is no longer recommended.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Tranexamic acid	IV	10mg-15mg/kg/dose	1g/dose	8hrly	1g/10mL Injection	For haemoptysis Discuss with Haematology	
Tranexamic acid	PO	12-25mg/kg/dose	1.5g	6-8hourly	Tablet 500mg	For haemoptysis	
Triclosan 1% w/v Pre-op wash	TOP	Use undiluted as body wash. Usually for 2 consecutive days		DAILY		For staphylococcal decolonisation	
Trimethoprim	PO	4mg/kg/dose	150mg/dose (Also may be given as 300mg daily for patients >40kg)	BD	Tablet 300mg Suspension 10mg/mL (CHW Manufactured item; by special order only)		
Ursodeoxycholic acid	PO	10-30mg/kg/day	30mg/kg/ Day	8-12 hourly	Capsule 250mg Suspension 50mg/mL	Common side effect is diarrhoea – reduce dose if occurs.	
Vitamin A (Retinyl Palmitate)	PO	0-3 years:1500-2000 IU/day >3 years: 2500-5000 IU/day Adjust according to serum levels.	5000 IU/dose	DAILY	Capsule 5000IU	Note that the usual multivitamin preparations used for CF are Pentavite/VitaABDEK and contain the fat soluble vitamins in the quantities required for prevention of deficiency in many patients. If child takes Pentavite,or Vitabdeck continue while supplementing for vitamin A & vitamin E.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Vitamin D (colecalciferol)	PO	Initial dose for treatment of deficiency: <12 months:400-500IU 12 months to 10 years: 800-1000 IU >10 years:800-2000 IU Please refer to Section 6.6.2 and Tables 6.6 and 6.7.	This must include ALL sources of Vitamin D Less than 12months: 2000IU 12months-10years: 4000IU Greater than 10yrs: 10,000IU	DAILY	Tablet 1000IU (OsteVit-D) Oral Drops 200IU/0.04mL drop (OsteVit-D) Solution 5000IU/mL (OsteVit-D)	Note that the usual multivitamin preparations used for CF are Pentavite/VitaABDEK and contain the fat soluble vitamins in the quantities required for prevention of deficiency in many patients. The Vitamin D doses in this table reflect additional requirements for treatment of deficiency in CF patients.	
Vitamin E (alpha tocopheryl)	PO	To prevent deficiency <12 months: Start 78 IU/day 1-7 years: Start 156 IU/day > 8 years: Start 250IU Adjust according to serum levels.	400IU/day	DAILY	Micelle E 156 IU/mL Cenovis Vitamin E: Capsule 250IU (250mg dl- alpha tocopherol acetate) Blackmores Natural E: Capsule 500 IU (335mg d- alpha tocopherol)	Caution: Take care when referring to literature as Vitamin E is available in various forms with variying potencies. (e.g. dl-alpha tocopherol acetate, d-alpha tocopherol) These doses reflect daily requirements in CF patients to prevent deficiency. Noting that the usual multivitamin preparations used for CF are Pentavite/VitaABDEK and contain the fat soluble vitamins in the quantities required. When dosing patients take into account the amount of vitamin E in their multivitamin preparation. If child takes Pentavite, or Vitabdeck continue while supplementing for vitamin A & vitamin E.	

Name	Route	Usual Dose	Max Dose	Frequency	Preparations	Comments	Reference
Vitamin K1 (phytomenadione)	PO	Infants and children: 1 - 2.5mg/day >12 years: 2.5-10mg/dose	Children less than 12 years: 5mg/day. Children greater than 12yrs: 10mg/day	DAILY	Capsule (Phytomenadione) 10mg Oral solution 2mg/mL	Dose guided by Gastroenterologist	
Voriconazole	PO	<2 years: 2-4mg/kg/dose 2-12 years: 9mg/kg/dose >12 years and <50kg: 200mg/dose for 2 doses then 100mg/dose >12 years and >50kg: 400mg/dose for 2 doses then 200mg/dose **(then as guided by levels)**	200mg/dose (unless loading in patients >50kg **and** >12years)	BD	Tablet 50mg Tablet 200mg Mixture 40mg/mL	ID approval required Check levels after 3 days to confirm absorption and no toxicity. Aim: 1 – 5.5mg/L Clinical signs of toxicity - hepatotoxicity, rash, visual changes and photosensitivity. Some patients may experience toxicity within therapeutic monitoring range.	4.7.3 4.7.4