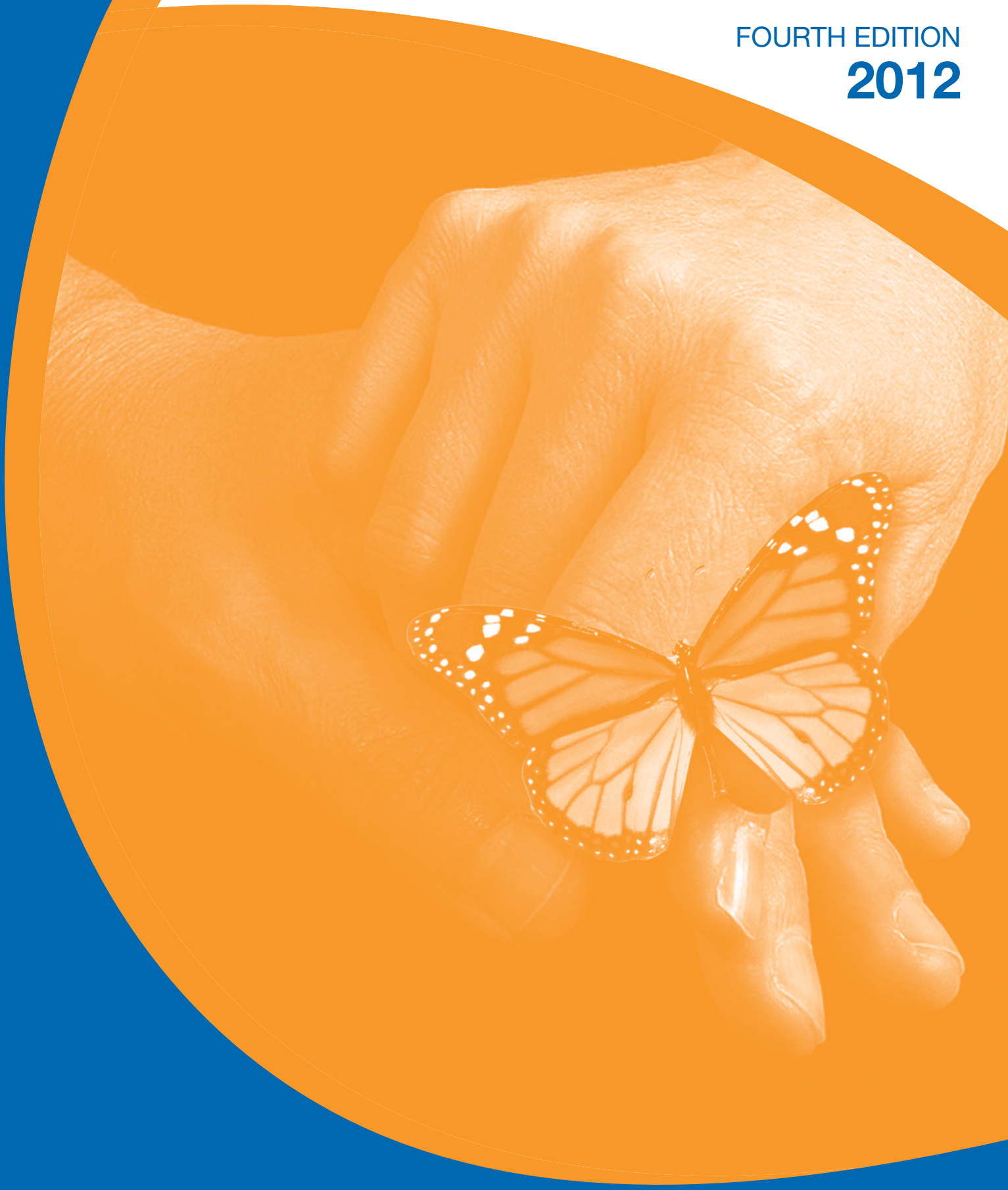
THE SOUTH AFRICAN CYSTIC FIBROSIS CONSENSUS DOCUMENT

FOURTH EDITION

2012



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AIM OF THE CYSTIC FIBROSIS CONSENSUS DOCUMENT

This document, although initially based on a European document, has been modified with input from SOUTH AFRICAN doctors who treat cystic fibrosis (CF) patients and scientists who have looked at the genetic basis of CF in SOUTH AFRICAN populations.

It is a consensus document detailing the diagnosis, appropriate treatment and counselling for the South African CF community. In general, South Africa offers services and expertise similar to those that are available worldwide for CF patients. Financial and staffing constraints present a challenge. The approach to this revision has been to search for new evidence in the areas of epidemiology, genetics, and clinical understanding of CF disease and its treatment. This evidence has been interpreted with a view to providing guidance for CF care in South Africa's health systems.

TARGET AUDIENCE

- CF patients and their families
- General practitioners and specialists diagnosing and treating CF patients
- Physiotherapists
- Dieticians
- Mental health professionals
- Health service administrators
- Hospital staff, and
- Counsellors.

The contents should guide the packages of CF care offered by Medical Aids and provincial health departments. It may be used as a reference text for teachers and employers.

SACFA
SOUTH AFRICAN CYSTIC FIBROSIS ASSOCIATION

Please contact the regional SACFA representative for further information or additional copies. (Contact information is given in Appendix 11 at the back of this document).

Acknowledgments:

Professor James Littlewood provided us with the initial document in the 1990s and many helpful comments during several visits to South Africa.

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(Dr Dave Richard, Dr Fanie Naude, and Ms Esta-Lee Tannenbaum contributed to the first and second editions.)

The valuable contributions of SACFA are gratefully acknowledged:
Mr Alan Dunn (President)
Mr George Pearson (late past Executive Officer)
Mr Alain Woolf (past President)

CONTENTS

1. INTRODUCTION

Cystic fibrosis is one of the more common life-limiting genetic diseases in South Africa. It is caused by the inheritance of at least two mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (see Chapter 3), is found in all of South Africa's diverse population groups. While incurable at present, its symptoms are amenable to good control when it is diagnosed early and managed appropriately, with the potential for a good quality of life into adulthood for many years.

1.1 THE BASIC PROBLEM

Cystic fibrosis (CF) is an inherited disease that results in many of the body's secretions becoming very sticky. The abnormal transport of salt across the body's surfaces (epithelial membranes and the skin) is a major factor causing these abnormal secretions.

Cystic fibrosis is associated with an increased amount of sodium and chloride in the sweat - usually more than 60mmol/l. This is the basis of the Sweat Test that is used to diagnose CF (see page*).

THE SWEAT TEST IS THE MOST IMPORTANT AND FREQUENTLY USED CLINICAL TEST FOR THE DIAGNOSIS OF THE CLASSICAL FORM OF CF

The most important practical problem in CF results from sticky secretions in the respiratory passages. There is an increased tendency to blockage of small airways and infections in the lungs. These chest infections, if not treated, become more severe and persistent, eventually leading to progressive lung damage and respiratory failure.

In the pancreas, the sticky secretions lead to blockage of the ducts with secondary damage to the secretory gland tissue, usually before birth. This results in deficiency of the pancreatic digestive juices, both enzymes and bicarbonate, causing severe intestinal malabsorption, threatening nutrition and growth. Fortunately, with modern pancreatic enzyme treatment, the majority of infants and children can grow normally and most have few gastrointestinal symptoms.

CF therefore is a life-threatening multi-organ disease, requiring continuous use of multiple therapies to prevent organ damage, and meticulous care by the patient, the family and the health team over a lifetime. A team approach within the framework of specialised CF centres is **essential** for optimal care. Every CF patient should have regular input from this team. Local health care professionals such as general practitioners and paediatricians should be part of a 'shared care' arrangement with these teams.

2. CLINICAL PRESENTATION AND DIAGNOSIS

Cystic fibrosis can produce many symptoms and clinical signs. Some are very much more common than others. This chapter describes the commonest presentations and some less common ones. A practical approach to its diagnosis in the South African setting is then set out.

It is important that CF is thought of in many clinical situations. The diagnosis requires special testing once the clinical symptoms and signs have led to CF being considered.

2.1 COMMON PRESENTATIONS

2.1.1 Meconium Ileus

In 15% to 20% of newborn CF infants, the bowel is blocked by sticky secretions. There are signs of intestinal obstruction antenatally on ultrasound, and soon after birth with bilious vomiting, abdominal distension and delay in passing meconium. The obstruction can often be relieved by Gastrografin® enemas, but some infants require surgery. The outlook for these infants is good as a result of the impressive improvements in neonatal surgery, anaesthesia and nutritional support.

2.1.2 Intestinal malabsorption / Poor weight gain

About 85% of CF individuals have malabsorption and in most cases this is evident in infancy. The main cause is severe deficiency of pancreatic enzymes and bicarbonate, although there is also evidence that the transport of some substances across the wall of the intestine is abnormal. These infants present with poor growth, failure to thrive and/or loose stools or steatorrhoea (offensive, fatty stools).

2.1.3 Chest infections

Virtually all CF patients have chest infections or wheezing, usually from an early age. The viscid mucus in the airways is particularly prone to bacterial infections, which, once established, are difficult to eradicate. Children with CF often have recurrent or chronic lower respiratory tract infections. Symptoms include persistent coughing that is often productive of sputum, and wheezing.

All three features may be present (‘classical cystic fibrosis’) but in a South African review, this was in a minority of cases (see Table 2.1).

2.2 PRESENTATION BY AGE

The Box shows the range of presenting features of CF. The commonest presentations involve the chest and the digestive system. It is important to note that many people with CF do not have growth problems at the time of diagnosis. **Normal growth does not exclude CF.**

Box 2.1: Presentation of cystic fibrosis by age.

2.2.1 Antenatal (with ultrasound scanning):

Thickened bowel wall (echogenic bowel)§
Bowel obstruction (dilated loops of bowel)§
Meconium peritonitis§

2.2.2 Newborn:

Meconium ileus*
Meconium plug§
Ileal and other intestinal micro-atresias§
Meconium peritonitis§

2.2.3 Infant and child:

Recurrent chest infections or wheeze§
Persistent chest symptoms/pneumonia with slow response to antibiotics§
Severe "bronchiolitis" §
Pseudomonas chest infection§
Uncontrolled "asthma" §
Bronchiectasis*
Chronic sinusitis¥
nasal polyposis
Clubbing§

Failure to thrive*
Conjugated hyperbilirubinaemia§
Anaemia, oedema and rash in infancy (mimicking kwashiorkor)*
Steatorrhoea/chronic diarrhoea*
Rectal prolapse*
Recurrent intussusception§

Salty tasting skin/salt crystals on the skin*
Hypochloraemic alkalosis§
Hyponatraemic dehydration/heat prostration§

2.2.4 Adolescent and adult:

Chronic obstructive airways disease§
Persistent chest symptoms/pneumonia with slow response to antibiotics§
Uncontrolled "asthma" §
Bronchiectasis§
Pseudomonas chest infection§
Sinusitis¥
Nasal polyposis*
Male infertility/azoospermia¥
Recurrent pancreatitis¥

*, §, ¥ - refer also to page * ("Making the diagnosis of CF")

The severity of presentation in CF can be very variable, even within a family.

2.2.5 Atypical presentations

- Male infertility (due to congenital bilateral absence of the vas deferens - CBAVD)
- Recurrent pancreatitis
- Chronic sinusitis
- Mild isolated bronchiectasis

In these cases, sweat tests may be negative or borderline, but mutations in both CF genes are present. This book does not deal with the management of these mild cases but rather with the classical sweat test positive cases.

2.3 MAKING THE DIAGNOSIS OF CYSTIC FIBROSIS

Most of the symptoms and signs above have causes besides CF. The following section will assist practitioners to know when and how to test for CF in South Africa.

When presented with a patient with a pattern of symptoms and signs for which CF is a possible explanation, the practitioner is in one of three diagnostic situations:

Typical CF probable **(clinical presentations marked with * in Box on page *)** – i.e. a high chance of CF being the cause; few other causes are likely to explain the symptoms; not to prove the diagnosis would be very likely to do the patient harm.

Typical CF possible (clinical presentations marked with § in Box on page *) – i.e. CF is but one of a set of possibilities in the differential diagnosis; it would be helpful to exclude it from the list if it were simple to do so.

*Atypical CF possible (clinical presentations marked with ¥ in Box on page *)* – there are symptoms that might be explained by another disease but do occur sometimes in CF, especially in late onset or late-presenting CF

2.3.1 Which test to use:

(Also see Figures 2.1 and 2.2)

1. **The sweat test (either electrolyte estimation or conductivity) remains the most important and frequently used clinical test for the diagnosis of the classical form of the condition.**

   Sweat Conductivity tests are more readily available but not as reliable as sweat electrolyte testing.
   Positive range for conductivity is 90 and above - refer.
   Levels between 50 and 89 (borderline/grey zone) should be discussed with a specialist in CF (see Appendix 11 p*).
   Level <49 - negative

   Sweat electrolyte testing:
   Positive range for chloride of above 60mmol/l;
   Levels of 30-60mmol/l should be considered to be grey zone/borderline and should be discussed with a specialist in CF (see Appendix 11 p*). The sweat

chloride level is almost always higher than sweat sodium in CF. Level <30 – negative.

2. Where sweat testing not available, the **faecal pancreatic elastase-1 test** can be used to demonstrate pancreatic insufficiency (PI). A level less than 100 mol/l indicates severe PI; levels from 100-200 mol/l indicate moderate PI. (See Figures 2.1 and 2.2 on page * for when to use this test.)
3. **Testing for CF-related gene mutations** on a blood specimen can be helpful. When to use this test is shown in Figures 2.1 and 2.2 on page *. (For further insights into CF genetic testing, see Chapter 3.)

The Diagnostic Algorithms on the page * indicate how to use these tests and the services available in South Africa to assist in making or excluding the diagnosis of CF depending on clinical presentation and availability of these diagnostic tests.

Figure 2.1: Approach to testing for cystic fibrosis where sweat testing is available

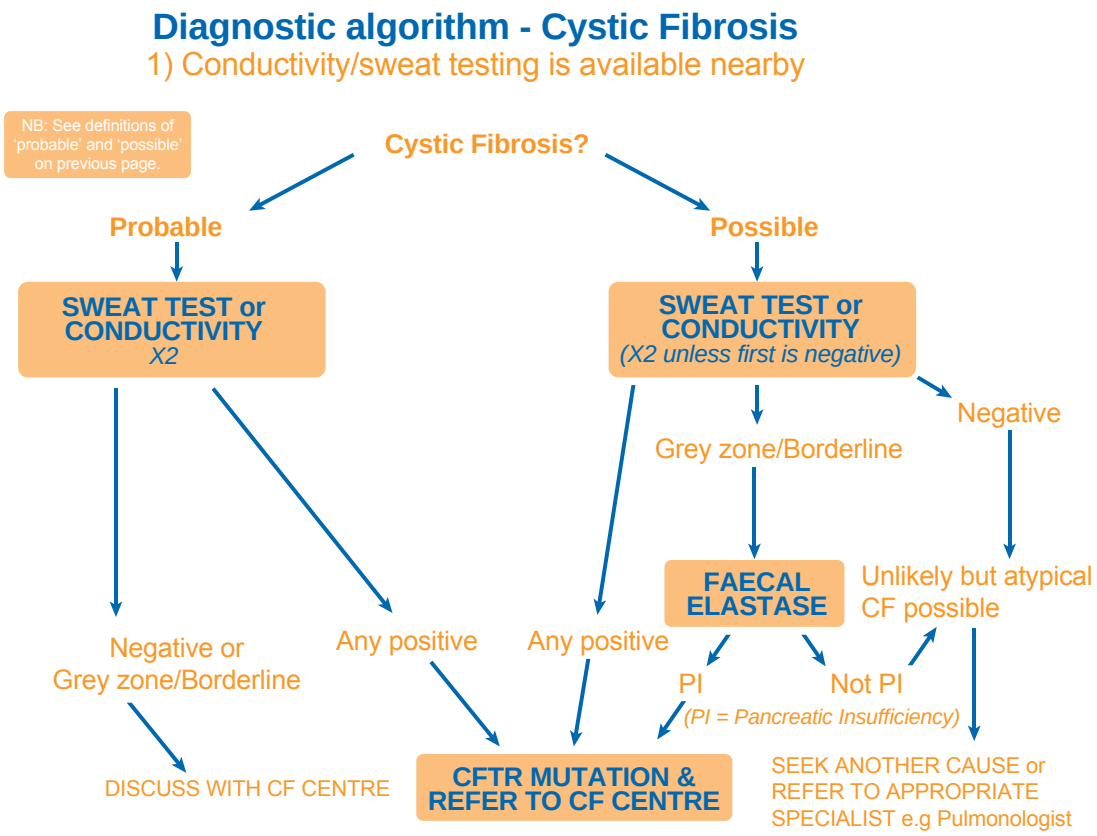
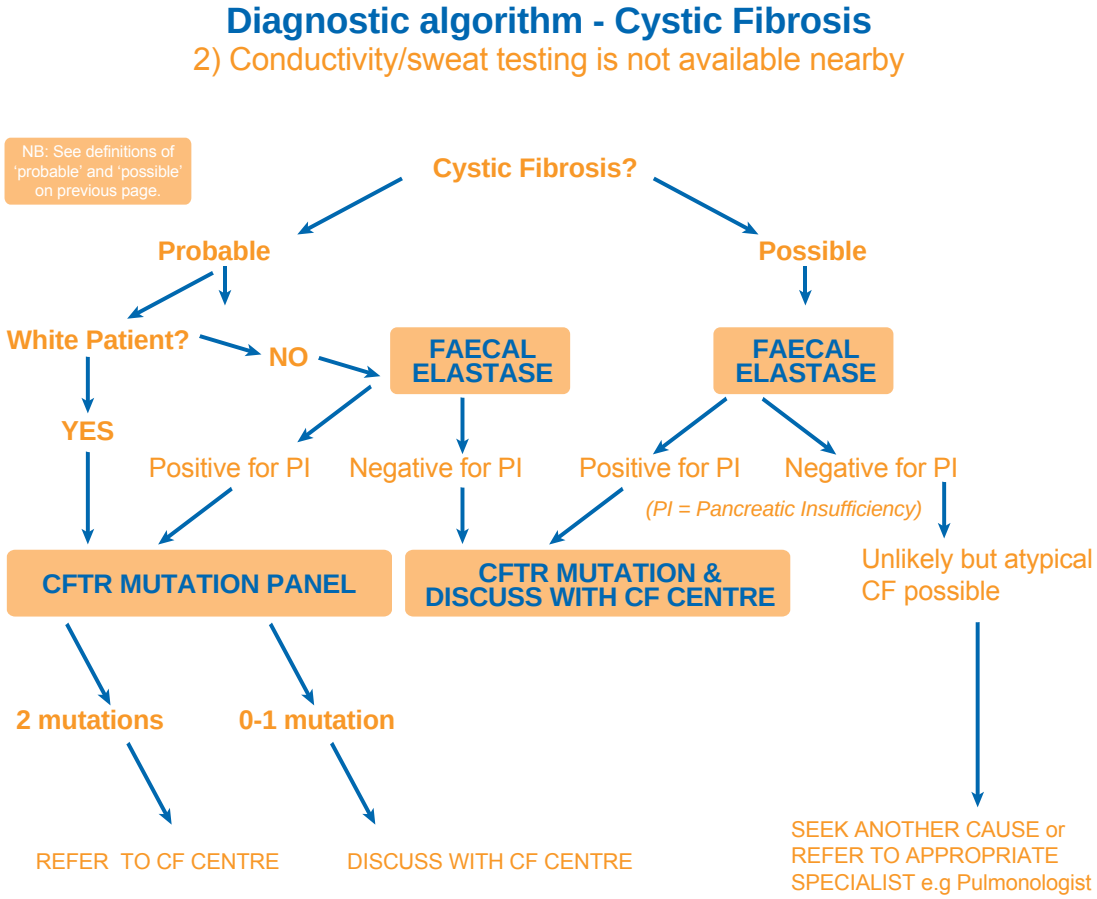


Figure 2.2: Approach to testing for cystic fibrosis where sweat testing is not available



Two positive sweat tests (performed by laboratory personnel experienced in the technique) should be done before a definitive diagnosis of CF is given. If the patient does not have two recognised CFTR mutations, a third sweat test should be performed a year or so later, **NO MATTER HOW CERTAIN THE DIAGNOSIS MAY APPEAR.**

It is advised that all CF patients have their blood examined to identify their CF-causing mutations. The regional CF Centre should be contacted for advice. Details are found in Appendix 11.

Mistakes in diagnosis do occur. Both over-and under-diagnosis are possible and repeat testing is often required.

Prenatal genetic diagnosis is discussed in Chapter 3.

Reference

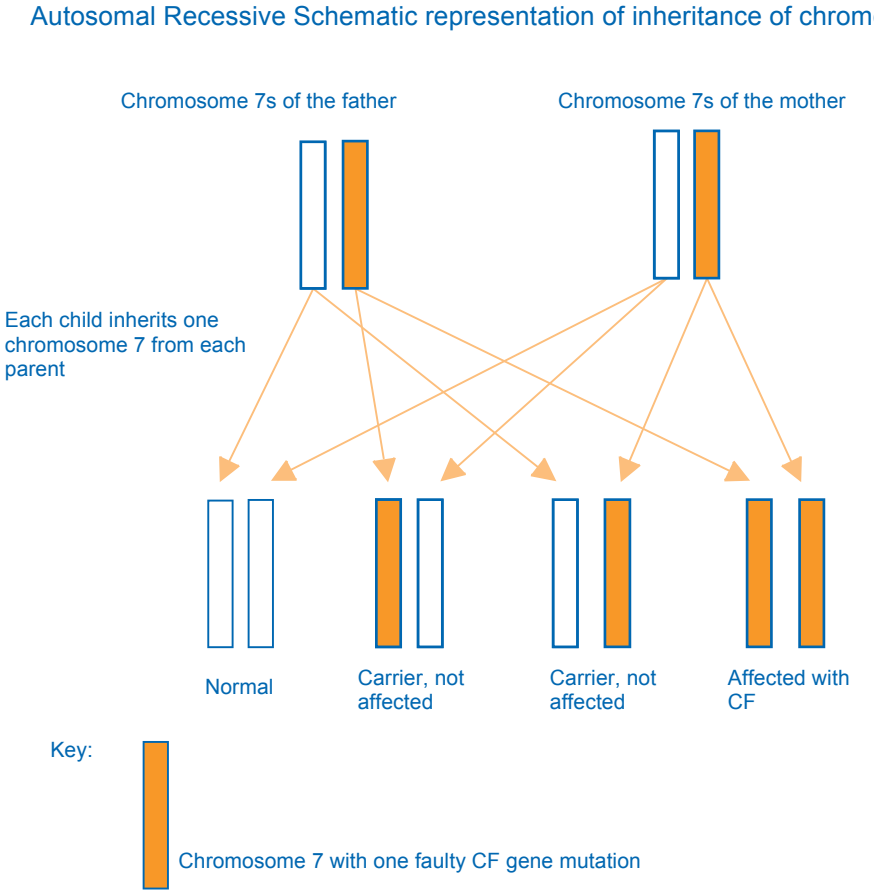
Farrell PM, Rosenstein BJ, White TB et al. Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report. Pediatrics 2008:153;S4-S14

3. GENETIC TESTING AND COUNSELLING

Cystic fibrosis is a genetic disease, inherited in an autosomal recessive manner. This means that affected individuals have a mutation in each of the two copies of the CFTR gene and that each parent of a child with CF is a carrier of one abnormal CF gene, but is individually healthy. When a child with CF is diagnosed, there is often no history of CF in either the mother's or father's families. The altered CFTR gene can be passed down in families in the carrier form for many generations without being detected.

In South Africa approximately 1 in 20 individuals in the white population, 1 in 55 in the population of mixed ancestry and up to 1 in 90 black Africans carry a CFTR mutation. Statistically it would be expected that 1 in every 2000 white babies, 1 in every 12 000 babies of mixed ancestry and up to 1 in every 32 000 black African babies should be born with CF. If a couple has a child affected with CF, each subsequent pregnancy that they have together has a 1 in 4 chance of producing a fetus/baby with CF. The parents are called *obligate carriers* of a faulty gene for CF (see figure 3.1).

Figure 3.1: Autosomal recessive inheritance of the faulty gene for CF, showing a 1 in 4 chance of having an affected child with every pregnancy



The CFTR gene has been identified on the long arm of chromosome number 7. More than 1800 different mutations have thus far been described. A mutation is a mistake or change in the DNA sequence of a gene that causes it to be unable to function correctly.

- The most common mutation in the white population and in the population of mixed ancestry ('coloured') in South Africa is the ΔF508 mutation.
- The most common in the black African population is the 3120+1G→A mutation.

It is important to know which mutation/s is/are present in a family with CF, especially when a sibling or other family members are planning their own families. If an individual tests positive for CF carrier status, their partner should also be tested to assess their risk of having a child with CF. Even if the specific mutation is not known within a family, it may be possible to predict who the carriers are by doing specialised tests. People who are unrelated to a person with CF may also be tested for CF carrier status and the majority of carriers will be detected. A blood sample is required for these tests.

In each population group, the distribution of the CF-causing mutations is different. Using the ΔF508 test only, about 80% of white carriers and 65% of carriers of mixed ancestry will be identified. It is estimated that approximately 46% of black African CF carriers will be detected using the 3120 +1G→A test. Patients with CF and their relatives have an increased risk of producing a child with CF when they have children.

Other individuals who may be at increased risk for having children affected with CF include more distantly related family members and couples from consanguineous marriages (marriages between related individuals). These individuals may be tested for CF mutations. In clinics for adults with CF, both CF patients and their children seem to be in favour of utilising the information available from genetic screening to guide reproductive choices.

To find out risks of having a child affected with CF, it is recommended that CF-affected individuals and their families see a genetic counsellor in order to accurately calculate risks to family members.

Reference:
Goldman et al. Molecular diagnosis of cystic fibrosis in South African populations. S Afr Med J 2003:93;518-519

3.1 PRENATAL DIAGNOSIS (diagnosis before birth)

Reliable prenatal diagnosis of CF is possible using chorionic villus sampling (CVS) or using amniocentesis. It is preferable that DNA testing of the parents prior to a baby's conception is conducted to determine the CF mutations that they carry. This makes the results of prenatal tests easier to interpret.

3.1.1 Chorionic Villus Sampling

CVS is an invasive prenatal procedure and is performed between 11 and 14 weeks of pregnancy. A small piece of the developing placenta is removed and the DNA

from this tissue is extracted and tested for the faulty CF genes. It is then possible to determine whether the fetus has CF. If the fetus is affected, there is the option of terminating the pregnancy. Alternatively, the parents may choose to continue with the pregnancy with the knowledge that the baby will be born with CF. The birth of this baby can then be planned with the necessary specialists in place. The CVS procedure carries a 2 to 3 % risk of miscarriage. The advantage of this procedure is that a result for CF could be obtained relatively early in the pregnancy so that pregnancy management can be discussed and organised timeously.

3.1.2 Amniocentesis

Amniocentesis is another prenatal procedure and that can be performed between 16 and 20 weeks of pregnancy. A small amount of amniotic fluid from around the fetus is removed. Cells in this fluid that originate from the fetus (containing fetal DNA) are tested for the faulty CF genes. Amniocentesis has a smaller risk for miscarriage than CVS (approximately 1%), but as this procedure is performed later in the pregnancy, decisions regarding continuation of the pregnancy, should the fetus be affected, may be more difficult.

3.1.3 Pre-implantation diagnosis

Pre-implantation diagnosis (i.e. checking at the very earliest stage of embryonic development whether CF is present) is at present only available at some specialist centres. Eggs and sperm are harvested from prospective parents who have already had a child with CF. Following the procedure of *in vitro* fertilisation, the developing embryos are screened at a very early stage for their CF status. Selected embryos, free of CF, are implanted into the mother's womb to continue their development.

Parents of a CF child who are planning to have more children and who wish to have antenatal tests performed to see whether the fetus has CF should consult with their doctor and with a genetic counsellor/geneticist before embarking on a new pregnancy. A list of Counselling Clinics around South Africa is found in Appendix 11.

3.2 SCREENING FOR CYSTIC FIBROSIS

Screening is the process of testing for a disease or health risk before it has caused a health problem. For a genetic disease like CF, this includes testing for carrier status.

3.2.1 Cascade screening:

Cascade screening is the term used for identifying carriers of a disease-causing mutation (such as those that cause CF). It occurs after the identification of an affected individual and the consequent genetic counselling of the family. The siblings of the affected individual and his/her parents can be screened for the presence of the mutation(s) identified in that family. Those who are carriers are then counselled about the implications and the tests that can be done on their partner. It is important that screening of siblings should only be done when the sibling is able to understand the implications of the test result i.e. capacity for consent must be assessed before the test is done. Generally this is best postponed to 18 years unless the sibling is sexually active.

When a mutation in a family is known, testing for the specific mutation can be offered. A negative result will exclude carrier status. A positive result confirms carrier status. The partner of a carrier (without a family history) can then be tested for the presence of a mutation. In this situation, a negative result does not exclude a carrier status, but can dramatically reduce the chance that it is present. A positive result confirms carrier status and allows the couple to make informed reproductive choices. The choices are the same as those that face the parents of an affected child. Genetic counselling is essential to allow such couples to make informed choices.

3.2.2 Newborn screening:

The purpose of newborn screening is to identify an infant who is at increased risk of having CF. Importantly, this screening test process is **not** a diagnostic test. A positive screening test must be followed up with a diagnostic test before a diagnosis of CF is made and treatment commenced for those infants who require it. No screening test is perfect and all yield a proportion of false positive results (i.e. test is positive but the infant does not have CF) and false negative results (i.e. the test is negative but the infant does have CF; the opportunity for early treatment is missed). All CF newborn screening is based on blood immunoreactive trypsin (IRT) and CFTR mutation analysis.

Cascade screening and antenatal testing of carrier couples is possible and available in South Africa. Broad-based population newborn screening for CF is being investigated, but it is not practical at present. Newborn screening using testing strategies of uncertain validity is available in some private laboratories in South Africa.

The following references can be consulted should more detail about strategies and other aspects of screening is desired.

Reference:
Wagener JS, Zemanick ET, Sontag MK. Newborn screening for cystic fibrosis. Curr Opin Pediatr 2012;24(3):329-35

3.2.3 Potential future drugs for CF treatment based on genetic mutations

There is no cure for CF, but progress is being made on the development of drugs that are aimed at CF individuals with defined mutations in the CF gene. As a result of increased knowledge of the consequences of some of the mutations at the cellular level, these drugs are being developed and trials are taking place in selected CF Clinics abroad.

The first drug for CF, targeted at individuals with a specific CF mutation, was approved by the US Federal Drug Administration (FDA) in January 2012. Kalydeco (previously known as VX-770) is approved for use in CF patients with the D551G mutation and who are over 6 years old. Another drug, Ataluren (previously known as PTC124A) is currently in the trial phase. It is targeted at mutations called premature stop mutations or nonsense mutations, and include W1282X, G542X, R1162X, E69X and W1262X. These mutations are, however, relatively rare and will

only be appropriate for a small group of CF patients. Phase 2 clinical trials combining Kalydeco (previously VX-770) & VX-809 in patients with at least 1 Delta F508 mutation are well underway & promising interim results were demonstrated in April 2012. Should this combination be successful, it would be suitable for the treatment of a significant proportion of CF patients.

The developments in mutation-targeted therapy highlight the need to identify the DNA mutations in CF patients in order to assess whether they would be suitable candidates for future treatments. For up to date information, visit the UK CF Trust website (http://www.cftrust.org.uk/) or the US CF Foundation website (http://www.cff.org/).

4. GENERAL MANAGEMENT AND APPROACH TO TREATMENT

4.1 GENERAL MANAGEMENT

The outlook for the individual with CF has improved dramatically. Many of the clinical features previously thought to be inevitable can be prevented, delayed or improved by intensive treatment. The introduction of a more positive attitude to management and the more widespread use of aggressive treatment regimes have been major factors in improving longevity and quality of life. Better survival is associated with more frequent use of antibiotics and more frequent review at CF clinics. As insulin is to people with diabetes, so are regular, high doses of antibiotics to people who have cystic fibrosis.

4.1.1 Communication at the Time of Diagnosis

It is difficult for parents and/or patients to obtain more than a general impression of the condition when it is explained for the first time. Not only is CF a very complex disorder but parents are usually shocked and unable to follow detailed explanations at that time. There is a need to consolidate the information they receive at their first visit.

A team approach must be followed. Clinic visits should include consultation with medical personnel, physiotherapists, dieticians, clinic sisters, pharmacists, social workers, psychologists and parent support groups.

Information must be made available to general practitioners, caregivers, teachers, relatives and friends. This information should be available in hard copy from the clinic. Additional sites of information, such as the Internet, may be of use.

It may be helpful for relatives to talk to the families of other affected individuals. Mutual support is generally most beneficial. "Remember, you are not alone".

4.2 GENERAL MANAGEMENT BY A NON-CF SPECIALIST

Some CF patients will be living far from a CF clinic and will find it difficult to attend CF clinics. They will be cared for by general practitioners (GPs) who do not have much experience with CF and who do not have ready access to the support of allied medical staff. It is essential that the GPs align themselves with the nearest CF Clinic and send their CF patient(s) at least yearly for assessment at the CF Clinic. Summaries of CF clinic visits should be sent to primary care doctors. As a relationship is built up with clinic doctors, so the GP will feel more comfortable about telephoning for advice and referring the patient when necessary.

4.2.1 General Facts Discussed at the Time of Diagnosis

- CF remains a serious disorder despite the major advances of recent years.
- The condition of the patient and the long-term outlook depends on the effectiveness and aggressiveness of the treatment and patient compliance is integral.

- The outlook continues to improve year by year.
- Individuals who have CF will always need regular follow-up at a hospital. The condition is so complex and advances in treatment so rapid that all patients must be cared for under the guidance of the CF specialist at the regional CF clinic.
- The hereditary aspects of CF.
- Families are told about the Cystic Fibrosis Association. If they agree, their names are forwarded to the relevant CF association. For contact addresses, see Appendix 11.

4.2.2 General Precautions for the Individual who has CF

There are a number of reasonable precautions that should be observed by the CF individual and the family:

- Immunisation is very important (see Section 4.3, p*).
- **NO SMOKING** (active or passive). Smoking is particularly bad for people with CF.
- Starting nursery school or crèche should be delayed (ideally until 3 years of age).
- Reduction of exposure to friends and relatives who have just started with a "cold" as this is when they are at their most infectious.
- If an infant with CF is admitted to hospital, every effort should be made to provide a cubicle to reduce the risk of acquiring an acute viral infection from other acutely ill children.
- Avoidance of close contact with stables, compost or other forms of rotting vegetation is advised because of the risk of the inhaling *Aspergillus* spores or infection by *Burkholderia cepacia*.

4.2.3 CF patients should attend a specialist CF Clinic

- Patients should attend a CF Clinic every one to three months.
- Here the patient's progress must be reviewed by the entire team, if possible.
- At every visit the patient must be weighed and measured.
- At every visit a sputum sample or cough swab should be sent for microscopy, culture and sensitivity.
- Parents should have a sputum container at home to send to the laboratory in the event of new respiratory infection or production of unusually purulent sputum.
- From the age of five years, spirometry should be performed (by experienced personnel).
- Oxygen saturation should be measured using a pulse oximeter.
- To avoid cross infection when using all respiratory function equipment, the use of bacterial filters is advised.
- All staff must wash their hands between patients.

- A comprehensive CF assessment is recommended at diagnosis and annually (see sections 4.2.4.and 4.4 respectively).

Reference:
Borowitz D et al.. CF Foundation Evidence Based Guidelines for the management of Infants with CF. J Pediatr 2009:155;573-593

4.2.4. Details of the Initial Comprehensive CF Assessment

History/examination
Anthropometrics (height, weight, etc)
Immunisation status
Family/personal smoking

Confirmation of diagnosis
Sweat test
DNA testing

Lung status and Tests
Respiratory function
Bronchodilator test
Physiotherapist's assessment
X-ray chest
Sputum culture
Aspergillus precipitins & RAST (depending on age and symptoms)
Total IgE

Gastrointestinal status
Dietician's assessment
Electrolytes

Faecal human pancreatic elastase 1 (at diagnosis)
Modified GTT (if >10 years or younger if losing weight or there are symptoms suggestive of diabetes mellitus)
Vitamin A, D, E serum levels (if available)
Adult diagnosis: ultrasound of liver and portal system

Additional tests
Full blood count
Liver function tests
Adult diagnosis: bone mineral density estimation

Other
Social worker consult
Genetic counselling (Section 3, p11), diagnostic testing of siblings.

Reference:
Kerem E et al for Consensus Committee. Standards of care for patients with cystic fibrosis: a European Consensus. J Cystic Fibrosis 2005:4;7-26.

4.3 IMMUNISATION

Normal childhood immunisations including pneumococcal vaccination should be administered since viral and bacterial respiratory tract infection can have a detrimental effect on the patient's lung function and disease progression.

An annual influenza vaccine covering the expected strains for that season should be given as a routine in March/April except if there has been anaphylaxis to egg.

Passive immunisation against the respiratory syncytial virus (Synergis®) for children under the age of 2 years is thought to be useful during epidemics.

Immunisation against chicken pox and hepatitis A is recommended.

A vaccine to *Pseudomonas aeruginosa* is under trial at present. When/If it becomes available it should be given prior to colonisation with the organism.

Reference:
Malfroot A et al for ECFS Vaccination. Immunisation in the current management of CF patients. J Cystic Fibrosis 2005:4;77-87

4.4 ANNUAL REVIEW

History/examination
Anthropometrics (height, weight, etc) and review of progress over the year
Immunisation status

Lung status and Tests
Respiratory function and review of the year
Physiotherapist's assessment
X-ray chest preferably a high resolution CT scan of the lungs every 2 years.
Sputum culture and review of the year
Full blood count
Total IgE, *Aspergillus* precipitins & RAST (depending on age and symptoms)

Gastrointestinal/Nutritional status
Dietician's assessment
Sodium, potassium, urea, creatinine, cholesterol, calcium, magnesium, alkaline phosphatase blood levels
Faecal human pancreatic elastase 1 if pancreatic sufficient at time of review
Modified GTT (if >10 years)
Vitamin A, D, E levels (if available)
Ultrasound of liver and portal system (>10 years)

Additional tests
Adults: bone mineral density estimation
Confirmation of both CF causing mutations re : future treatment modalities.

Other
Social worker review
Review and discussion of genetic/family issues.

The results of assessments and tests should be discussed with the patient and/or parents. Included in the discussions should be:

- Current health status
- Meaning of the changes (if any) over the year reviewed (good and not-so-good news)
- Adjustments to treatment regimes for the coming year
- Aims of the adjustments
- Discussion of the patient's CF care in general
- Planning for life events in the coming year e.g. school, employment

5. MANAGEMENT OF RESPIRATORY PROBLEMS

5.1 INTRODUCTION AND OVERVIEW

Lung disease is the primary cause of morbidity and death in CF patients. Bacterial infection and host inflammatory response in the airway begins early in life and leads to progressive structural lung damage. Clinical manifestations of CF lung disease are highly variable in onset, rate of progression and severity. Management should aim to minimise structural lung damage through early diagnosis, good nutrition, minimising exposure to viral respiratory infections, ensuring adequate immunisation, avoidance of smoking (active and passive) and most importantly, early use of appropriate *antibiotics* and *physiotherapy*.

5.2 MONITORING LUNG DISEASE

A standardised approach to monitoring CF lung disease is important and should begin from the time of diagnosis. Early detection and treatment of deterioration lung disease or infections may delay or prevent irreversible structural lung damage.

5.2.1 Clinical:

Regular attendance (3-4 monthly) at a CF centre is critical to effective monitoring and early intervention. A careful history should be taken at every visit to elicit any symptoms suggestive of new or exacerbating infections. Careful revision of physiotherapy techniques and medication (inhaled and oral) should be undertaken at every consultation. Although insensitive at detecting early or minor changes, a thorough physical examination (including upper respiratory tract) is important to detect new or advancing respiratory disease. Hyperinflation or air trapping is a reliable sign of peripheral airways obstruction that is frequently present even in young children.

5.2.2 Pulmonary function testing

Spirometry repeated at every visit is the standard approach to objectively measuring lung disease. It is useful for identifying trends, detecting acute changes in lung function and monitory response to treatments. Standard flow-volume parameters such as FEV_1 and FVC are the most reliable measurements. Despite optimal treatment, a rate of FEV_1 decline of 1-2% per annum is expected. Early changes of peripheral airway obstruction may be detected by reductions in FEF_{25-75}. Any decline in pulmonary function should be evaluated in the context of the individual patient and not that of the population norms.

Spirometry is possible in children 6 years or older but may be attempted in children as young as 3-4 years of age. Pulmonary function measurement is difficult in infants and young children and is currently not routinely performed in most CF centres.

5.2.3 Sputum microbiological surveillance

Regular (3-4 monthly) monitoring of respiratory tract cultures is critical for identifying and treating pulmonary infections. Early detection and eradication of *Pseudomonas aeruginosa* will delay chronic infection. Adults and children older than 6 years can usually voluntarily expectorate. Sputum induction with nebulised hypertonic (3-5%)

saline is useful in those who are unable to expectorate. Oropharyngeal or cough swabs should routinely be performed in young children even if asymptomatic. A positive culture for *Pseudomonas* from a cough swab does not necessarily indicate lower respiratory infection with *Pseudomonas*. However, a negative culture makes lower respiratory tract infection very unlikely. Bronchoscopy and BAL culture is not indicated in the routine care of CF patients. They should be reserved for circumstances where identifying specific or unrecognised infections will influence antibiotic management and when good quality sputum specimens cannot be obtained by usual methods.

5.2.4 Imaging

Early structural changes in the CF lung long precede the development of symptoms and are poorly detected by physical examination or chest x-rays. Nonetheless, annual chest radiographs should be performed to detect obvious changes or trends in lung structure or volumes. Unless clinically indicated (e.g. atelectasis, pneumothorax), frequent and repeated chest x-rays should be avoided when patients present with repeated pulmonary exacerbations. CT scan is the most sensitive technique to monitor structural changes in the lung. However, high cost and significant radiation exposure (especially to children) prevent CT from being useful in the routine monitoring of CF lung disease.

5.3 AIRWAY CLEARANCE AND AEROSOLISED THERAPIES

5.3.1 Physiotherapy

Physiotherapy does not just refer to airway clearance techniques. It involves education and practical application with regard to the holistic assessment and management of the patient both at the time of diagnosis and subsequently as an evolving process throughout the patient's life.

Aspects of management include:

- Exercise
- Airway clearance prescription
- Musculoskeletal management
- Inhalation therapy
- Maintenance of correct weight
- Life choices
- Equipment choice and maintenance
- Infection control practices
- Medications
- Secondary complications (e.g. incontinence, osteoporosis)
- Quality of life.

5.3.2 Airway clearance techniques (ACT)

Airway clearance techniques form an integral part of the treatment for CF. This facilitates the loosening, mobilisation and clearance of the often thick and tenacious sputum to prevent airway obstruction and respiratory complications, and to maintain

or improve pulmonary function and ventilation. Lung hygiene can be boring, time-consuming and tedious. Therefore it must be effective, efficient, specifically designed for each individual and constantly modified and adjusted.

Infants

In infants, modified postural drainage, percussion, and thoracic compressions remain widely used, but other techniques such as infant positive expiratory pressure (PEP) therapy and assisted autogenic drainage (AD) along with physical activity (e.g. bouncing on a ball) have emerged as feasible alternatives.

The association of gastro-oesophageal reflux (GOR) and postural drainage (PD) using a head down tipped position, has led to a significant change in practice internationally. Many centres now advocate only the use of modified PD positions such as supine 300 head up, alternate side-lying, prone horizontal and supported sitting. Physiotherapy is performed before meals, or two hours after a meal, to prevent reflux and vomiting.

The role of routine airway clearance in asymptomatic infants has been questioned. There is however strong evidence for the presence of very early lung disease in terms of inflammation and infection, reduction in lung function, and structural changes even in “pre-symptomatic” infants. A cough should not be stimulated in an asymptomatic child, but imitation of a cough should be encouraged from the start of treatment. From early on in life (about one year of age) components of the active airway clearance techniques should be encouraged using playful blowing activities e.g. blowing bubbles encourages deep thoracic expansion and provides PEP with pursed lip breathing (PEP) during exhalation.

Conventional Chest Physiotherapy

Conventional chest physiotherapy (i.e. postural drainage and percussions/vibrations) was the mainstay of airway clearance for people with CF for many years, and was shown to be effective. However, it was also time consuming, required a second person to administer the chest manipulations, and has been associated with significant complications, especially when using the head-down PD position. Currently, conventional chest physiotherapy is generally only recommended for infants, those unable to comply with active airway clearance therapy (e.g. advanced disease), or if there is a specific patient preference. PD may be used in conjunction with other airway clearance techniques if indicated in specific patients in order to drain secretions proximally, and optimise ventilation and perfusion (breathing and blood supply) patterns to the lung. Head-down tilt is no longer advocated as side-lying positions are as effective and less likely to cause GOR, hypoxia or dyspnoea.

Active Cycle Of Breathing (ACBT)

The active cycle of breathing techniques consists of breathing control (BC), thoracic expansion exercises (TEE), and the forced expiration technique (FET or huffing). It can be adapted to individual needs, performed in any position, is effective and efficient in the mobilisation and clearance of secretions and improvement in lung function, and is not dependent on an assistant. If an assistant is present, chest percussion or vibration can be combined with the TEE. It can be performed by all patients who can follow instruction and is useful in all stages of the disease.

Autogenic Drainage (AD)

Autogenic drainage is a three-phased breathing exercise that can be done in any position. Breathing out actively (but not forced) from varying lung volumes helps to "unstick, collect and mobilise" secretions. It is not a forced technique and could be suitable for patients who show a decrease of oxygen de-saturation during physiotherapy or those with irritable, unstable or hyper-reactive airways, as airway closure is avoided. It requires concentration and sensitivity to breathing levels and the location of mucous. But young children can be taught to "play" with different breathing levels and the feeling or sound of moving secretions.

Pep Therapy

Applying a resistance during expiration by using a PEP mask or valve or by blowing gently (not prolonged or forced) into the bottom of a bottle containing 10 to 20 cm of water can help mobilise secretions. Good infection control measures must be taken with "Bottle PEP". The bottle and tubing must be rinsed and air dried after each session, and both must be replaced regularly.

Both PEP and Oscillatory PEP are contra-indicated if there is frank haemoptysis or a non-drained pneumothorax, and should be used with caution if there is raised intracranial pressure, acute sinusitis, active haemoptysis, oesophageal varices, middle ear pathology, recent facial, oral or oesophageal surgery, haemodynamic instability, drained pneumothorax or an inability tolerate the increased work of breathing.

Oscillatory Pep Therapy

Oscillatory devices vibrate the expiratory airflow which is thought to decrease the visco-elasticity of the sputum, loosen the secretions and improve mucous clearance, while preventing collapse of the airways. Frequencies between 8–16 Hz have been found useful for airway clearance.

Flutter (BronchuVibe): A small plastic device containing a large ball bearing which repeatedly interrupts the outward flow of air, and produces a resistance of 10-25 cmH2O and a range of airflow oscillation frequencies from 2–32 Hz.
Acapella: This uses a counterweighted plug and magnet to produce a resistance of 7-35 cm H2O and a range of airflow oscillation frequencies of 0–30 Hz.
Cornet: A horn-shaped tube which houses a rubber inner tube. The inner tube uncurls as the individual blows through it (like a party pooper but without the noise and with slightly more resistance).

High Frequency Chest Wall Oscillation (HFCWO Or The Vest)

An electric air compressor connects to an inflatable jacket (vest) to vibrate the chest pneumatically. The vest is extremely expensive and is reliant on electricity.

The choice of airway clearance method and device should be based on patient preference, compliance with therapy and effectiveness and efficiency of the therapy. There is no significant evidence to suggest that any of these devices are more effective than other techniques.

5.3.3 Mucolytics

Hypertonic saline:

Hypertonic saline (5-7.5%) has been evaluated and shown to benefit some patients. It can be helpful where secretions are particularly tenacious. It is by far the most cost-effective mucolytic. This therapy should be initiated under controlled conditions, monitoring for bronchospasm, although generally safe in most patients.

RhDNase:

RhDNase (Pulmozyme®) represents an important treatment for CF patients and good clinical trials have demonstrated that it works well and is safe. An improvement of 5-7% in lung function can be achieved but the high cost is a limiting factor.

Optimally rhDNase should be available in selected patients with demonstrable responsiveness to the drug in whom the FEV_1 is <70% of expected. RhDNase should only be used as an add-on therapy to patients on established pulmonary treatments. Ultrasonic nebulisers should not be used for rhDNase.

Other Mucolytics e.g. N-acetyl cysteine:

These are of no proven benefit but some patients feel better using them.

Mucolytics should be used alone in the nebuliser and not mixed with other medication. See also Appendix 5.

5.3.4 Nebulisers, compressors and aerosolised medication

Aerosolised medication should preferentially always be delivered by pressurised metered dose inhalers (pMDIs) or dry powder inhalers (DPI). Lung deposition with pMDIs or DPIs is superior to nebulisation, especially in children. An appropriate nebuliser is however essential for inhaled medication such as mucolytics and antibiotics that are available only in solutions. Patients with advanced lung disease may require a nebuliser for bronchodilator delivery. A mouthpiece is the preferred route of delivery when using a nebuliser. Children using facemasks should switch to a mouth piece as soon as possible. Patients should sit comfortably during nebulisation and be encouraged to breath normally with occasional deep inhalations. Lung deposition is negligible in a crying child using a facemask.

The amount of time required to deliver inhaled medications is important in CF. The faster the drug delivery, the better the compliance with treatment. It is essential that the correct nebuliser is used to deliver CF-related drugs. Inappropriate use will result in destruction of the inhaled drug and thus complete negation of the drug, or the need for higher doses to achieve the same effect. There are essentially three types of nebulisers (see Box). These have been listed below with associated advantages and disadvantages related to CF.

Box 5.1 Nebulisers used in cystic fibrosis

Nebuliser type	
Ultrasonic nebuliser	Inexpensive, fast These systems continuously release the drug throughout the respiratory cycle, so 60% to 70% of drug is wasted during expiration. patients are required to have a regular breathing pattern Destroys inhaled antibiotics and RhDNase Can only be used for inhaled bronchodilators, normal and hypertonic saline.
Jet nebulisers **PARI® TurboBoyS** **PARI® Junior Boy**	Robust Appropriate for all CF related nebulised medications Expensive and relatively time consuming

Vibrating Mesh Nebulisers **PARI® eFlow Rapid (VMT)** **Respironics® i-Neb** I-Neb (ADD)	This technology is very quiet, completely portable and efficient. Shorter treatment times are achieved, and there is less drug wastage Appropriate for the nebulisation of all CF-related medications Adaptive aerosol delivery (AAD): These new generation nebulisers are faster and quieter and the AAD provides detailed monitoring including date, time, completeness of dose and time taken to nebulise. AAD systems detect pressure changes during breathing and constantly adapt to the inspiratory and expiratory flow pattern of the patient. Expensive I-Nebuliser not available in SA

Cleaning and maintenance of nebuliser equipment.

Nebuliser tubing, mouthpieces, masks, and the reservoir should be thoroughly cleaned after each use using warm soapy water, then dried with paper towel and allowed to air dry completely. Twice weekly the disposable nebuliser components should be disinfected either by boiling in water for 5 minutes (if the manufacturer's recommendations allow for this); immersing items in 1:50 household bleach solution (5.25%-6.15% sodium hypochlorite) for 10 minutes; or microwaving items for five minutes. Bleach solution should also be nebulised for 10 minutes to ensure sterilisation of the jet. Following disinfection, the nebuliser components should be thoroughly rinsed (preferably with boiled, sterilised water) and allowed to air dry. Acetic acid is no longer recommended as a disinfectant as it does not adequately kill organisms such as *S aureus* and *E coli*.

Disposable nebuliser reservoirs with jets should not be used for more than three months. Ideally they should be changed once a month and long-use (durable) nebuliser reservoirs and jets should be changed once a year. The filters on the compressor should be changed when they become discoloured.

Order of delivering inhaled medications:

The order of use of the medications is important. The following recommended order of inhaled medication should be carefully explained to patients:

1. Mucolytics (hypertonic saline/RhDNase) before airway clearance techniques/chest physiotherapy.
2. A bronchodilator (β2 agonist) may be necessary in some patients at this stage to prevent bronchospasm.
3. Airway clearance and chest physiotherapy
4. Inhaled antibiotics, corticosteroids and long-acting β2 agonist should be used after the airway clearance techniques are concluded, and the coughing decreased.

5.3.5 Exercise

There is a growing body of evidence showing that those affected by CF are not only affected by decreased cardio-respiratory fitness but also decreased muscle power, strength and endurance. Further, poor posture and decreased flexibility are common features.

Exercise programmes should be:

- Individually tailored
- Frequently evaluated

- Integral part of the lifestyle of those with CF.

Physical training programmes must be enjoyable and should incorporate a range of types of exercise:

- Aerobic
- Anaerobic
- Strength training
- Flexibility
- Posture instruction.

Aerobic exercise should be ideally performed at least three days per week, for 30 minutes (broken into shorter intervals if required), with an increase in heart rate to approximately 75% of maximum, which equates to a perception of moderately hard exertion. Resistance training using low weight, high repetition training on alternate days, three days a week is recommended.

If osteoporosis or osteopaenia is suspected, care must be taken in prescribing weight training. Similarly, weight training should only be introduced after adolescence. Modification of exercise will be necessary during periods of acute infection, if there is hypoxia, and following surgery. Prolonged exercise may increase the risk of dehydration and hyponatraemia which could lead to increased mucous viscosity.

In patients with CF-related diabetes, prolonged exercise may increase the risk of hypoglycaemia. As the disease progresses, patients may be at increased risk of exercise induced de-saturation and may require supplementary oxygen if oxygen levels fall below 90%.

The short and long term benefits of regular physical activity are well established and the importance of regular, enjoyable, physical exercise as an essential part of the physiotherapy regimen is recognised. Subjective measures of perceived exertion or breathlessness should be used to gauge the level of exercise.

5.4 RESPIRATORY INFECTIONS AND INFLAMMATION.

Impaired mucociliary clearance, bacterial infection and neutrophilic inflammation are the hallmarks of CF lung disease. These changes begin in infancy even before the development of symptoms or clinical evidence of structural airway damage. Peripheral airway obstruction, intermittent cough and sputum production is common. Bacterial pathogens are frequently isolated in the sputum of CF patients. Treatment depends on the specific pathogen and clinical context in the individual patient. Management includes early recognition and treatment of new or significant infections, preventing chronic infections and long-term prophylactic antibiotics where certain chronic infections are established.

5.4.1 Overview of Pulmonary exacerbations/acute infections

A pulmonary exacerbation is defined as an episode of increased cough and sputum production often accompanied by decline in pulmonary function and systemic symptoms such as lethargy, anorexia and fatigue. Fever is uncommon; **however, a change in the cough pattern is the most sensitive early sign for a new or increasing infection.** The symptoms are often less obvious and the respiratory signs may be subtle, especially in young children. Auscultation of the chest with a

stethoscope is unreliable for detecting exacerbations as crackles and wheeze are common even in CF patients without pulmonary exacerbations. Other symptoms and signs that suggest an increase in activity of airway infection are:

- reduced or absent weight gain or, more significantly, loss of weight
- a change of sputum colour from white to yellow or green
- a change in sputum quantity and smell, and/or
- New infiltrates or changes on a chest x-ray. Chest rays are not required to diagnose pulmonary exacerbations are should not be performed with every exacerbation.

A sputum (or cough swab in non-expectorating patients) should be obtained with every exacerbation and sent for routine CF bacterial cultures. Viral and mycobacterial investigations should be requested if indicated.

The management of a pulmonary exacerbation will depend on several factors:

- The severity of symptoms. Generally, mild exacerbations i.e. absence of systemic symptoms, are initially managed with **oral antibiotics (2 weeks)**. **Intravenous antibiotics** are indicated for more severe exacerbations or when there has been an unsatisfactory response to oral antibiotics. Intravenous antibiotics should be administered **for a minimum of 2 weeks** in the hospital or home-setting (*see Section 5.4.8 page * on Administering IV antibiotics).*
- Bacteriology: Treatment is guided by which bacterial or other pathogens are isolated in the patient's sputum and whether the patient is chronically infected (colonised) with certain pathogens or not. In cases where no bacterial pathogen has been identified, the choice of antibiotic should be determined by the most likely bacteria given the patients age and circumstances. *Note:* Growth of *S aureus*, *P aeruginosa* or *Aspergillus* in the sputum from a colonised patient who does not have new symptoms does not represent an exacerbation and does not always require treatment. (see section 5.4.2)
- Institutional and individual or family preferences and resources.

5.4.2 Overview of Chronic infection/colonisation

Although chronic bacterial infection and airway inflammation is inevitable present, chronic airway infection with specific pathogens like *Pseudomonas aeruginosa* or *methicillin resistant staphylococcus aureus (MRSA)* is associated with increased morbidity and a more rapid deterioration of lung disease. A patient should be regarded to as colonised with a specific pathogen if, despite eradication attempts (if applicable), the organism is isolated in 2 or more consecutive sputa within a six month period. Vigilant sputum surveillance to detect early infection by these pathogens is thus important to prevent chronic infection or colonisation. When first detected, aggressive antibiotic treatment to eradicate these pathogens is necessary (see *Eradication protocols section 5.4.5*).

Long-term management of patients colonised with *Pseudomonas* in whom eradication is unsuccessful is aimed at suppressing infection and inflammation through **prophylactic inhaled antibiotics** (gentamycin, tobramycin, colistin) **and anti-inflammatories** e.g. low dose azithromycin. The benefit of long-term

macrolide therapy in the absence of *Pseudomonas* colonisation has not been well established and is still under investigation (see section 5.4.7).

Chronic infection by CF-associated pathogens is acquired in an age-dependent fashion However, increased vigilance and aggressive antibiotic therapy should result in delayed acquisition and colonisation of *Pseudomonas*.

5.4.3 Common CF-associated pathogens:

The clinical significance and management of common CF-associated bacterial infections is summarised in the table below. The route of antibiotic administration and need for hospitalisation will depend on the severity of symptoms and must be individualised in every patient.

The clinical relevance and management of common CF pathogens is presented in table 5.1.

Table 5.1 Management of common pathogens in cystic fibrosis

Pathogen	Clinical significance	Management
Haemophilus Influenzae	Early infection common and colonisation not associated with long term detrimental effects.	**Asymptomatic**: no treatment
		Exacerbation: amoxicillin, co-amoxiclavulanic acid Alternatives: 2nd generation cephalosporin, one of the newer macrolides. Intravenous therapy if severe exacerbation or symptoms.
Staph aureus	Early infection and colonisation is common but not associated with worse long-term outcomes. Chronic infection of the respiratory tract by *S aureus* can be postponed by the use of prophylactic anti-staphylococcal antibiotics. However this may allow early infection with *P aerugi-nosa*. The risk of bacterial resist-ance to the antibiotic will also be raised by prolonged continuous use.	**1st or new infection**: only treat if associated with new symptoms or exacerbation.
		Asymptomatic colonisation: no treatment
		Exacerbation: ***Oral:*** First line: Flucloxacillin or cloxacillin Alternatives: Macrolides, clindamycin, cephalosporins (1st or 2nd generation), cotrimoxazole.ed continuous use.
		IV: Cloxacillin or 2nd generation cephalosporins e.g. Cefuroxime
MRSA	Evidence emerging recently that, like *pseudomonas*, colonisation with MRSA is associated with poorer long term pulmonary function. Increasing prevalence worldwide attributed to increased antibiotic usage and repeated exposure to healthcare facilities. Strict infection control measures are advised to prevent crossinfection.	**1st or new infection:** attempt eradication regardless of symptoms (*see section 5.4.5*). Screen family and staff. Implement strict infection control measures where possible. Topical mupirocin (Bactroban®) recommended for treatment of superficial infection sites in carriers e.g. nasal passages.
		Asymptomatic colonisation: no treatment

Continued on next page

Pathogen	Clinical significance	Management
Haemophilus Influenzae	Family members and health care workers should be screened if MRSA is isolated from a patient.	**Exacerbation:** choice of antibiotics depends on sensitivities (discuss with microbiologist). ***Oral:*** Drugs include rifampicin (not alone), fusidic acid (not alone) and linezolid. Cotrimoxazole may be useful in community acquired MRSA. ***IV:*** vancomycin, teicoplanin or Linezolid (preferred in serious in infection). Monitor vancomycin drug levels to prevent toxicity and ensure therapeutic levels are achieved. Inhaled: nebulised vancomycin IV solution can be considered. Anecdot (preferred in serious in infection). Monitor vancomycin drug levels to prevent toxicity and ensure therapeutic levels are achieved. Inhaled: nebulised vancomycin IV solution can be considered. Anecdotally reported to be effective and well tolerated.
Pseudomonas aeruginosa	Pseudomonas infection is always significant and colonisation with mucoid P. aeruginosa is associated with increased morbidity, poorer lung function and long-term survival.Acquisition of Pseudomonas infection may asymptomatic, particularly in young children. Initially Pseudomonas is nonmucoid and highly antibiotic sensitive. Without early treatment, mucoid strains will predominate and eradication then becomes very difficult. Regular sputum (or cough swab) surveillance, and aggressive eradication therapy when first detected will postpone colonisation.	**1st or re-infection :** eradication *regardless of symptoms*(see section 5.9) **Exacerbations:** ***Oral:*** ciprofloxacin for 2 weeks. Oral ciprofloxacin has few side effects although photosensitive skin rashes may occur. Cartilage problems have not been documented in humans and are not a contraindication to using the drug in children. Ciprofloxacin should not be used in CF patients who are pregnant ***IV:*** traditionally 2 antibiotics, usually a combination of an aminoglycoside plus ceftazidime or cefipime is used. *A minimum of two weeks is strongly recommended.* Antibiotic blood levels should be done when using aminoglycosides (trough ~ toxicity; peak ~ efficacy) Alternatives: carbapenems, piperacillin/ tazobactam or ciprofloxacin are used according to sensitivities and patient tolerance. Carbapenems ideally should not follow quinolones within the same antibiotic course as resistance is likely to occur. Fourth generation cephalosporins such as cefepime can be given as a continuous infusion. This may reduce bacterial resistance and is costeffective. The doses must be large as CF patients tend to utilise some drugs, including antibiotics, more rapidly than normal (see Appendix 2). Improvement during a course of IV treatment can be demonstrated by performing regular respiratory function tests and carefully assessing the other signs including body weight.

Continued on next page

Pathogen	Clinical significance	Management
Multidrug resistant (MDR) pseudomonas	Frequent antibiotic use, either for prophylaxis or treatment of exacerbations, is associated with the risk of resistance. However frequent high dose antibiotic therapy is an essential part of CF management. Acquisition of MDR Pseudomonas may be associated worsening symptoms. Strict infection control measures are advised to prevent cross-infection.	***1st*** or re- infection: attempt eradication with inhaled antibiotics and 2 weeks adjuvant IV therapy (no effective oral agent) if previously Pseudomonas-free regardless of symptoms. Asymptomatic or stable colonisation: It is recommended that prophylactic inhaled antibiotics (gentamycin, tobramycin, colistin) continue even if there is laboratory resistance to the antibiotic as the concentration delivered to the lungs is very high. Anti-inflammatories e.g. low-dose macrolide e.g. azithromycin
		Exacerbations: The choice of antibiotic treatment of exacerbations is influenced by bacterial susceptibilities. Successful treatment may still occur when antibiotics to which the organism is resistant are used. Where aminoglycoside resistance occurs they should still be used in combination with another class of antipseudomonal agent as synergy can occur rendering the combination more effective than the non-aminoglycoside agent on its own.
Respiratory viruses	The role of respiratory viruses in the pathogenesis of CF lung disease is not known. Viral infections are common and a frequent trigger for exacerbations or bronchial hyper-reactivity (wheeze or asthma) by 'stoking' underlying bacterial infections and airway inflammation. Antibiotic therapy is therefore usually indicated. The choice of antibiotic needs to be individualised. Identification of viral pathogens in respiratory samples (nasopharyngeal aspirate or sputum) may help avoid unnecessary antibiotics and guide management, especially	Mild URTI only: treat symptomatically. Consider withholding antibiotics if spontaneous recovery likely.
		Exacerbations: - In young children who are free of colonising organisms, co-amoxyclavulanate or a 2nd generation cephalosporin (e.g. cefuroxime) is the antibiotic of choice. -Oseltamivir (Oral/IVI) if Influenza virus suspected. - Consider inhaled bronchodilators, short course oral corticosteroids or leukotriene receptor antagonist if significant lower airway obstruction or wheezing, especially if reversible.
		Prevention: Hand washing and avoidance of close contact with individuals with colds. Young children should preferably not attend large crèches or day-care facilities. Annual Influenza vaccination is recommended.
No known bacterial pathogen	Pulmonary exacerbations and significant lung disease does occur where no pathogen is identified. Infection with viruses and other common organisms e.g. S Pneumoniae or Mycoplasma may co-exist in CF.	The choice of antibiotic should be determined by the most likely bacteria/pathogen given the patients age and circumstances. Past sputum cultures should be reviewed to guide antibiotic therapy. Oral: co-amoxiclavulanic acid or 2nd generation cephalosporin or newer macrolides e.g. azithromycin (older children and adults). IVI: Ampicillin and cloxacillin; or cephalosporins or co-amoxiclavulanic acid.

5.4.4 Uncommon CF pathogens

5.4.4.1 *Aspergillus*

Aspergillus (all species) is a ubiquitous environmental fungus that rarely causes disease in immunocompotent healthy people. The CF lung is however an ideal growth medium for *Aspergillus* Its spores are equally ubiquitous thus avoidance of inhaling the spores is difficult. CF patients should ideally avoid situations where there is an increased risk of inhaling these spores: stables, compost and other forms of rotting vegetation.

Cultures of sputum from patients with CF often yield *Aspergillus* species, but for most patients without allergic symptoms, the presence of *Aspergillus* does not seem to affect the clinical course. At the present time, no special treatment is recommended for these patients but some transplant centres recommend suppression of *Aspergillus* with itraconazole or voriconazole. ABPA is a complex hypersensitivity reaction that occurs when bronchi are colonised by *Aspergillus* species. (See section 5.5.3 on page * for ABPA)

5.4.4.2 *Burkholderia cepacia*

It was originally thought that *Burkholderia* was a single species. With advances in bacterial genetics it is now known to constitute multiple separate species, each of which is a member of the *Burkholderia cepacia* complex (BCC). The species most commonly isolated from the sputum of CF patients are *B multivorans* and *B cenocepacia*.

Chronic infection with BCC is associated with an accelerated decline in pulmonary function and shortened survival in CF, the so-called ‘cepacia syndrome’. Evidence for patient to patient spread is strong and has led to recommendations for stringent infection control measures within CF care centres. These bacteria are often highly resistant to multiple antibiotics. Lung transplantation in patients infected with BCC is associated with recurrent and often severe infection with poor outcomes particularly for those carrying *B cenocepacia*. Infection with this organism is considered to be a contraindication to transplantation in many centres. However, some patients appear to have transient isolates of BCC.

Treatment options with antibiotics are often limited, but some isolates show sensitivity to co-trimoxazole, doxycycline, ceftazidine and/or meropenem,

doripenem. When no single antibiotic is effective, combinations of two or more antibiotics sometimes show in vitro sensitivity.

5.4.4.3 *Non tuberculous mycobacteria*

Non-tuberculous mycobacteria (NTM) can be isolated in the sputum of approximately 13% patients with CF. *Mycobacterium avium intracellulare* (MAI) is identified in up to 75% of these patients. The other frequently isolated pathogen is *M abscessus* which grows rapidly and is found in up to 16% of NTM-positive patients with CF.

NTM may either exist as a commensal causing no harm. On the other hand, it may be a pathogen. NTM disease should be considered under the following circumstances:

- systemic symptoms,
- deteriorating pulmonary function
- appearance of nodular opacities and/or cavities on chest radiograph or High Resolution CT scan (HRCT).

Once a NTM is isolated in the sputum, further sputa should be submitted to see if it is repeatedly isolated. If it is, a HRCT should be performed to detect nodules or cavities. If these are present or if the lung function is deteriorating despite standard intensified treatment, treatment directed at NTM should be seriously considered.

Eradication of MAI is difficult and requires 24 months of treatment with rifampicin, ethambutol and clarithromycin. *M abscessus* is particularly difficult to treat and needs a combination of cefoxitin, amikacin, clarithromycin and possibly linezolid. Infection with MAI seems to have no adverse impact on patients with CF undergoing lung transplantation. On the other hand *M abscessus* infection can cause soft tissue and mediastinal abscesses that can recur despite drainage and antibiotics.

5.4.4.4 *Mycobacterium tuberculosis* (MTB)

With the high prevalence of tuberculosis (TB) in South Africa, CF patients may develop either pulmonary or extra-pulmonary tuberculosis. TB should be considered in any CF patient with unexplained weight loss or night sweats. The chest radiograph may not be helpful in view of the changes related to CF.A HRCT of the chest though may reveal cavitation or nodules. Positive acid fast bacilli in the sputum should be distinguished from NTM by routine culture and molecular techniques. Drug-susceptibility testing should routinely be performed. Treatment is the usual four drug therapy, but if the CF patient has overt liver disease pyrazinamide should probably be omitted.

5.4.4.5 *Stenotrophomonas maltophilia* and *Achromobacter xyloxidans*

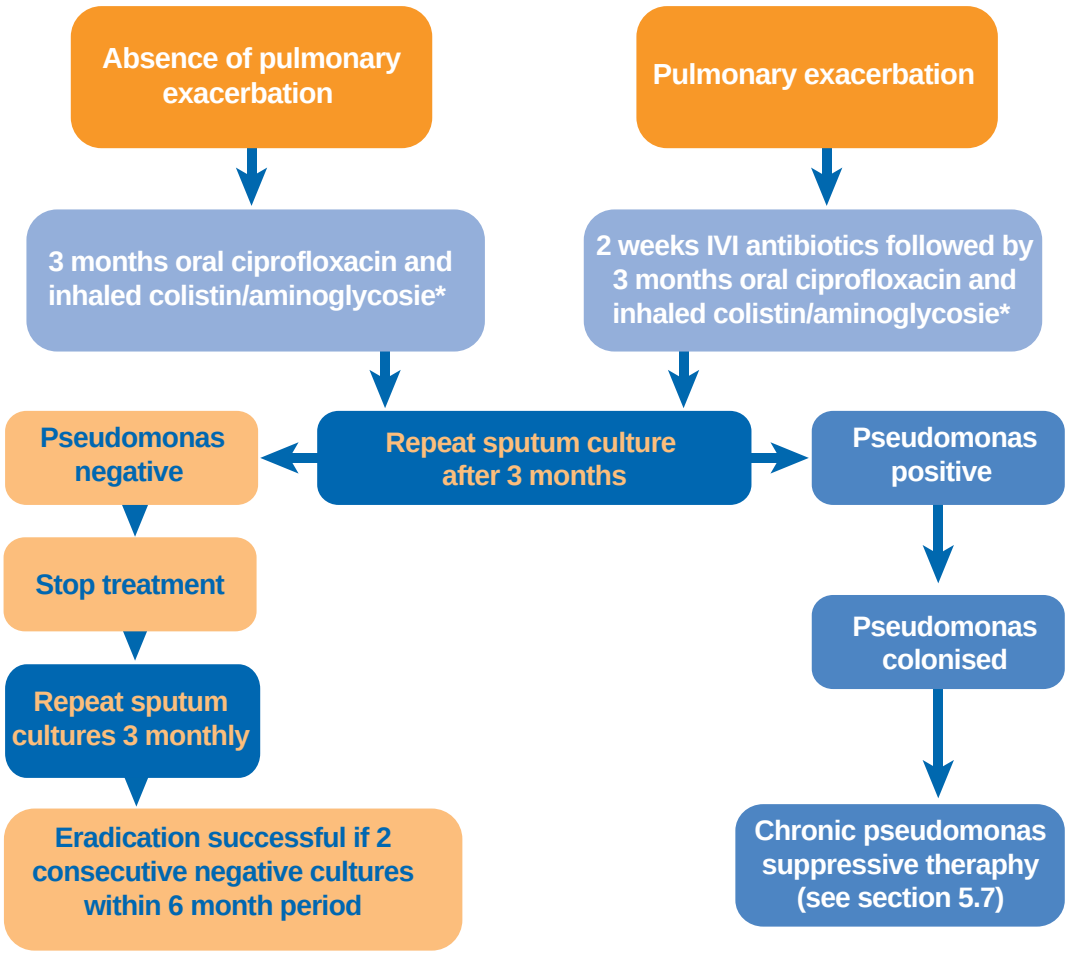
During the past decade, gram-negative organisms other than *Pseudomonas* such as *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans* have become increasingly found in CF patients. These organisms are inherently resistant to most standard antibiotics. The impact on the natural history of CF lung disease appears to vary among individuals.

5.4.5 Eradication of significant infections

5.4.5.1 *Pseudomonas aeruginosa*

Chronic airway infection with *Pseudomonas* is associated poorer lung health and survival. Acquisition of *Pseudomonas* may occur early in life and is often asymptomatic. Early detection through regular surveillance and aggressive eradication treatment will delay or prevent chronic *Pseudomonas* infection. Many eradication protocols are practised throughout the world. None has been shown to be superior over others. Inhaled aminoglycoside therapy delivers very high concentrations of antibiotic into the airway without systemic absorption. Eradication can be deemed to have been achieved if, despite monthly sampling, the organism is not cultured within six months. Reappearance of the organism (or a rise in anti-pseudomonal antibodies) thereafter necessitates reinstitution of the regimen set out below. Persistent infection despite eradication attempts implies colonisation/chronic infection. Management hereafter aims to suppress chronic *Pseudomonas* infection by continuous intermittent use of inhaled antibiotics and anti-inflammatories i.e. azithromycin.

The following *Pseudomonas* eradication protocol is recommended for the South African setting:



**** 3 months low-dose azithromycin (i.e. anti-inflammatory dose) may be added to the eradication regimen.***

5.4.5.2 *Methicillin resistant staphylococcus aureus (MRSA)*

MRSA isolated from either upper or lower respiratory tract samples should always be regarded as significant. Eradication treatment after first detection will depend on the patient's symptoms and availability of antimicrobial agents. Several non-evidence based eradication protocols have been reported with anecdotal success. The protocol in Box 5.2 is an example:

Box 5.2 protocol for the eradication of *Methicillin-resistant Staphylococcus aureus*

At first detection of MRSA: Respiratory and multi-site swabs (Nose, mouth, groin, other orifices)

a) Hygiene advice is given to patients and their parents/carers at the start of the treatment course and includes advice on:
   - changing bed linen at the start of treatment
   - use of own towel, face cloth and toothbrush
   - replacement of all nebulisation components and sterilization of this equipment

STEP 1:
- Topical mupirocin 2% to anterior nares twice daily for five days
- Chlorhexidine for washing (body, hair etc)

If respiratory sample MRSA positive:
- Sodium fusidate 50 mg/kg/day for five days
- Rifampicin 20–40 mg/kg/day for five day

b) Respiratory and Multi-site swabs (Nose, mouth, groin, and other orifices) are repeated for detection of MRSA on completion of treatment step 1 and again at each clinic visit for up to one year after last isolation of MRSA.

If MRSA persists then proceed to step 2
STEP 2: – Repeat above protocol for a further five days

If MRSA persists then proceed to step 3
STEP 3:
- Intravenous teicoplanin 10–15 mg/kg/daily 12h x three doses; then
- Intravenous teicoplanin 10–15 mg/kg/daily once daily for nine to 13 days

c) Respiratory samples and multi-site swabs are repeated for detection of MRSA on completion of treatment step 3 and again at each clinic visit for up to one year after last isolation of MRSA.

d) Alternative antibiotic strategies:
   - Oral cotrimoxazole and fusidic acid or
   - Oral linezolid, or
   - Inhaled vancomycin (IV preparation)

5.4.6 Management of chronic infections/colonisation

5.4.6.1 Prophylactic antibiotic therapy in the chronically infected patient

There is good evidence that regular therapy with an inhaled antibiotic reduces the rate of deterioration of lung function in CF patients chronically infected with *Pseudomonas*. Gentamicin, tobramycin or amikacin (the intravenous forms) by inhalation are widely used in South Africa seemingly with good effect. Colistin and a special formulation of tobramycin (TOBI®) have been shown to have beneficial effects. These two antibiotics are considerably more expensive. In choosing an antibiotic sensitivity of the organism should be used as a guide.

Aerosolised antibiotics

Nebulised antibiotics have an established place in the management of CF. Their major use is in attempting to prevent chronic infection and to control established chronic infection when it occurs.

Although colistin is the antibiotic used in most of the initial studies on this mode of therapy, it has no clear advantage over aminoglycosides (tobramycin, gentamicin, and amikacin) or other anti-pseudomonal antibiotics (provided they can be nebulised). The choice of antibiotic is usually based on the bacterial sensitivities found on sputum culture (although these results do not always equate to in vivo efficacy).

Nebulised antibiotics do not cause toxicity (systemic absorption of aminoglycosides in one study was only + 0.5% of the dose). Nebulised antibiotics often cause some degree of bronchoconstriction (related mainly to hypertonicity of the solution and/or possibly preservatives) so it is recommended that they be administered after a bronchodilator. (Note: The bronchodilator is best administered via an MDI with or without a spacer device and not a nebuliser. This technique reduces the time needed for nebulisation therapy and increases patient adherence.)

In order to facilitate maximal deposition of drug in the lungs for as long as possible, the following are recommended:

- Administer nebulised antibiotics after sputum clearance (physiotherapy + RhDNase or hypertonic saline)
- Use a mouthpiece. Small children may require a mask.
- Breathing at a relaxed tidal volume through the mouth (rather than “big breaths”)
- Use a suitable nebuliser and compressor: The best being an active Venturi nebuliser (breath assisted) with a 6 l/min flow rate.

Preparation of antibiotics for nebulisation

Standard IV preparations of antibiotics are used in South Africa. The solutions should be reconstituted with sterile water or saline to a volume of 4mls. The preparation of isotonic solutions of colistin appears in Appendix 4.

Reference:
Campbell PW, Saiman L. Use of Aerosolized Antibiotics in Patients with Cystic Fibrosis. Chest 1999;116:775-788

5.4.7 Anti-inflammatories

Inflammation plays a major role in lung disease in CF. .The level of inflammation directly correlates with the progression and outcome of the disease. The anti-inflammatory treatment modalities that have been most tested are: oral corticosteroids, inhaled corticosteroids, ibuprofen and macrolides.

5.4.7.1 Corticosteroids

The therapeutic efficacy and safety of several oral and inhaled corticosteroids have been evaluated in children with CF, but the precise mechanism through which these agents control inflammation and affect CF pulmonary disease has not been elucidated.

Oral corticosteroids

Prednisone and prednisolone are oral glucocorticoids with potent anti-inflammatory effects. Prednisone has effectively controlled the inflammation of CF pulmonary disease; however, although effective, the utility of corticosteroids in the treatment of CF pulmonary disease is limited by long-term safety concerns. Prolonged prednisone therapy for suppression of inflammation cannot be recommended for children with CF. When indicated, prednisone should be administered in the lowest effective dose for a limited time. When corticosteroids and itraconazole are administered simultaneously to treat allergic bronchopulmonary aspergillosis, patients must be monitored for symptoms suggestive of drug-related adverse events.

Inhaled corticosteroids

Inhaled corticosteroids are better tolerated and produce fewer adverse effects than systemically administered forms. Of the five available inhalation corticosteroids, beclomethasone, budesonide, and fluticasone have been evaluated in children with CF.

In patients with CF, the fraction of the dose ultimately reaching the site of the most severe inflammation may be poor given the viscous, mucus-lined epithelium through which it must pass. In children, the drug may never reach its primary site of action, which may account for the lack of efficacy demonstrated by inhaled corticosteroids in controlled clinical trials. Inhaled steroids thus can only be recommended in CF where CF-related asthma is present.

5.4.7.2 Ibuprofen and other non-steroidal anti-inflammatories

Ibuprofen has been shown on a number of studies to improve lung function and nutritional indices compared to controls. High dose ibuprofen has been advocated as an anti-inflammatory agent for treating patients aged 5 years or older with CF whose predicted FEV_1 is 60% or greater.

The recommended initial dosage is ibuprofen 20–30 mg/kg twice/day, titrated as needed to a dosage that produces a peak plasma concentration of 50–100 µg/ml based on pharmacokinetic monitoring.

Data concerning safety and efficacy after long-term therapy with high-dose ibuprofen in CF are lacking. However, serious adverse effects such as gastrointestinal bleeding limit the routine use high dose of ibuprofen in CF and it is thus no longer recommended. Short courses may be prescribed to treat pain and musculoskeletal inflammatory conditions.

5.4.7.3 Macrolides

Many studies have shown that macrolides may have beneficial properties besides antibacterial activity in several chronic lung diseases including CF. Several macrolides have been studied but azithromycin seems to have most potent effect, acting as a long-term anti-inflammatory agent with an excellent safety profile. Several studies have reported improvements in pulmonary function and body weight after treatment with azithromycin compared with placebo. Patients on azithromycin also appear to have less risk of exacerbations. Treatment with erythromycin or clarithromycin has not been shown to be beneficial in CF.

There are conflicting reports on the benefit in young patients who are not infected with *Pseudomonas*. The efficacy of macrolide treatment in patients with *B cepacia* and those not colonised with *Pseudomonas* is unknown.

The emergence of macrolide-resistant non-tuberculous mycobacteria is of concern. Patients should be assessed for NTM before and every six months after initiating azithromycin therapy. Organism sensitivities should also be monitored with regular sputum culture (3-6 monthly)

Azithromycin therapy for up to 6 months appears to be safe; nausea, diarrhoea, and wheezing are the predominant adverse effects. The latter may possibly be caused by the mobilisation of secretions. Continuing therapy seems necessary to maintain the benefits associated with azithromycin therapy.

Recommendations at present based on data currently available:

- Azithromycin rather than other macrolides
- Patients chronically infected with *P aeruginosa* above 6 years of age
- Suggested dosage: 15 - 40 kg: 250 mg 3 times/week
  >40 kg: 500 mg 3 times/week

5.4.8 Administering intravenous antibiotics and Venous Access

(Indications for intravenous antibiotics are given in Section 5.)

5.4.8.1 Hospital intravenous antibiotic therapy

It is important to stress that the “hospital treatment package” should include:

- removal from the home environment
- some rest,
- temporary transfer of the responsibility of treatment from the patient/family to the hospital staff,
- nutritional assessment and intervention
- regular meals with possible increased adherence to pancreatic enzyme replacement therapy and vitamin supplements
- physiotherapy
- psychosocial evaluation and intervention

The duration of a course of intravenous therapy varies but must not be less than two weeks. The frequency of courses varies between patients. Usually a combination of an aminoglycoside plus ceftazidime or cefipime is used in patients infected with *Pseudomonas*. Other antibiotics are used according to sensitivities. The doses must be large as CF patients tend to utilise some drugs, including antibiotics, more rapidly than normal (see Appendix 2).

Repeat clinical and pulmonary function assessment after the hospital admission should be done to demonstrate any beneficial effect.

5.4.8.2 Home intravenous antibiotic therapy.

Many studies have demonstrated that adequately supervised home IV antibiotic treatment is a practicable, effective and acceptable alternative to hospital treatment for many CF patients. Some patients have the first few days of treatment in hospital and complete the course at home. Adequate support and training of the caregivers is essential. Antibiotic blood levels should be done where appropriate and IV technique reviewed.

At the end of the two-week course of home IV antibiotics, the patient ideally attends the CF Unit:

- Respiratory function tests are performed
- Sputum is obtained
- The patient should also be seen by the doctor
- Physiotherapist.
- The CF team decides whether maximal improvement has occurred and whether further treatment is required.

Simple cost effective devices may make ambulatory home and school based IV therapy practical. The Springfusor pump (Cobros Medical Supplies) provides one such option.

Totally Implantable Venous Access Devices (TIVADs) (e.g. Port A Cath® or Implantofix®, Braun®) have proved valuable in overcoming problems of venous access for many patients having regular IV antibiotic therapy. It is essential that both family and professionals are familiar with the use of these devices. Complications limit their use and peripheral IV sites remain a first choice where possible. Supervised follow-up must be meticulous.

5.4.8.3 Venous access

Peripheral intravenous cannulae are the preferred option for venous access. Distal veins should be used where possible. For children, topical anaesthetic creams should be applied prior to siting intravenous cannulae.

When peripheral access becomes difficult, alternatives are needed. Peripherally inserted long lines (PICC lines) or Midlines can be placed. Silastic catheters may remain *in situ* for extended periods. They are easy to handle and are often preferred by patients. The use of such catheters should be considered as an alternative in ambulatory IV treatment.

Whilst peripherally inserted long lines (PICC lines) and Midlines can be used, in many cases access will eventually be problematic. Insertion of a Totally Implantable Venous Access Device (TIVAD) or "Port" makes venous access easy and takes away the stress on the part of the patient and doctor on deciding whether to give intravenous antibiotics.

A Port is placed in theatre under a general anaesthetic with the catheter from the Port inserted in a subclavian vein. The device is inserted on the upper anterior chest wall and when low profile is aesthetically acceptable. Immediate screening of the chest and/or a chest radiograph should be done to exclude a pneumothorax which is a possible complication of inserting a port. The port is accessed by a non-coring port needle either ½ inch or ¾ inch in length.

The benefit of a Port outweighs the disadvantages.

Complications of TIVADs

The major concern is the introduction of **infection** which may lead to septicaemia or even endocarditis. Absolute aseptic precautions are required when using the port. A port infection is usually recognized by the presence of rigors and fever within 20-40 minutes of injecting through the port. If a port infection is suspected the needle should be removed and a new needle inserted and blood attempted to be withdrawn from the port. In addition 2 peripheral blood cultures should be taken. The port should be removed at the earliest opportunity and the outlet cannula sent for culture. It is advisable to wait two weeks or so for the infection to settle before inserting a new port.

The other main problem encountered with a port is blockage. This can be prevented by flushing the port with 1-2ml in 1000u heparin after each antibiotic infusion and when not in use by flushing the port monthly with heparin. The monthly flushing can be done by a trained nurse or doctor or the patient can be trained to insert the port needle his or herself and flush the device. At all times a non-coring needle should be used.

Other possible complications include:

Venous thrombosis and even **superior vena cava syndrome** although these are very uncommon.

Dislodgement of the catheter. This is suspected when injection is accompanied by pain and difficulty in injecting. It is advisable to always inject the port with a 10ml syringe rather than a 5 or 2.5 ml syringe as the injection pressure is less with the larger syringe and therefore less likely to cause a disconnection. If this complication does occur an interventional radiologist will be required to retrieve the detached catheter.

Leakage. This is recognized by pain and a swelling around the port on injection.

Air embolism. Ensure there is no air in the lines. Using a Clave connector on the port will prevent air being sucked in but the needle should also be closed with the clamp when not in use preventing any risk of an air embolism.

In general ports are well accepted by CF patients and their convenience and ease of use outweighs any disadvantage. A port enables a CF patient to readily have home based intravenous antibiotics with as least disruption to their lives as possible.

Reference:
Buck C. Holl R. Kohne E. Wolf A. Silastic catheters: An alternative to the conventional peripheral venous infusions access in patients requiring IV therapy for an extended period for home antibiotic therapy in patients with cystic fibrosis: European Journal of Pediatrics. 1997;156(3):209-211

5.4.9 Infection Control and Prevention

The two major sources of acquiring pathogenic organisms are from the natural environment and health care facilities. **Infection through environmental sources is however the most common route.** Transmission of organisms can also occur through contact with contaminated medical equipment, other CF patients and infected medical staff.

Respiratory tract pathogens are transmitted through one of three routes:

- Direct or indirect contact with infected secretions or surfaces.
- Large droplets which are suspended in air for short periods and transmitted within a distance of one.
- Airborne spread of small droplet nuclei which remain suspended in air for long periods.

Strategies in different settings to prevent acquisition or transmission of pathogenic organisms include:

- In the home and surrounds:
    - Avoidance of environments likely to harbour *Pseudomonas* e.g. warm and wet indoor facilities, or *Aspergillus* e.g. compost heaps or stables.
    - Meticulous cleaning and disinfecting of medical equipment such as spacers, PEP devices and nebuliser accessories.
    - Siblings should ideally have separate nebulisers and medical devices. Ideally, they should also sleep in separate bedrooms where possible.
    - Routine immunisations including annual influenza vaccination should be encouraged.

- In the ward
    - Standard infection control measures and precautions should be adhered to at all times.
    - Patients should ideally be segregated from other CF and non-CF patients, especially if infected with organisms such as *Pseudomonas aeruginosa*, BCC, MRSA and respiratory viruses.
    - Patients and medical staff should be encouraged to use high filtration masks.
    - Good cough etiquette should be encouraged.
- In the clinic
    - Cohort segregation based on sputum culture results is not always feasible or desirable. However, patients infected with MRSA, BCC or multidrug-resistant *Pseudomonas* should preferably be segregated from non-infected individuals.
    - Patients should sit at least 1 metre apart in the waiting areas.
    - Waiting areas, lung function and physiotherapy rooms should be well ventilated and clean. Sputum collection should also take place in well ventilated spaces and sputum containers must be sealed immediately after use.
    - Pulmonary function equipment must be cleaned between patients and new disposable filters used with each patient. Patients should wipe their hands with disinfectant before they hold the lung function equipment.
    - Patients with MRSA, BCC, multidrug-resistant *Pseudomonas* and mycobacterial infections should perform lung functions last.
    - Health care workers should wash and disinfect their hands and stethoscopes between patients.

Reference:
Morrow BM, Whitelaw A, Zampoli M Westwood AT: Infection Control in Cystic Fibrosis: Recommendations for South African hospitals, clinics and social environments. South African Respiratory Journal Vol 16 No 1

5.5 RESPIRATORY CO-MORBIDITY AND COMPLICATIONS

5.5.1 Sinusitis and nasal polyposis

Chronic rhino-sinusitis (RS) and/or nasal polyposis occurs in 50% of CF patients with up to 100% upper airway abnormalities of the upper airway (UA) seen on CT scan. Despite this acute purulent sinusitis is uncommon. Self reported incidence of RS in CF is as low as 10%. There is increasing evidence that the UA is a site of first colonisation and a reservoir of *Pseudomonas*.

Regular examination for nasal polyposis is needed. If the polyps are symptomatic, nasal steroids should be tried. If this fails, surgical treatment is indicated and should preferably be undertaken by a surgeon who is familiar with CF. The gold standard of sinonasal radiographic imaging is a CT scan.

Acute sinusitis should be treated with topical steroids and antibiotics as dictated by sputum cultures. Patients with chronic sinus symptoms such as headache and congestion should be referred to an ENT surgeon who is skilled in functional endoscopic surgery, the management of choice for chronic sinusitis. In the short term, surgery leads to significant improvement of symptoms but benefits only persist in 50% and recur in 46-100% in 2 to 4 years and therefore a more aggressive surgical approach is used in CF patients.

Allergic rhinitis may occur in CF patients and especially in the atopic patient with asthma. Standard guidelines-based treatment principles for allergic rhinitis should be followed. Topical corticosteroids form the basis of this therapy. Older antihistamines should not be used.

Reference:
Gysin C, Alothman GA, Papsin BC. Sinonasal disease in cystic fibrosis: clinical characteristics, diagnosis, and management. Pediatr Pulmonol. 2000;30(6):481-489
Mainz J, Koitschev A. Management of chronic rhinosinusitis in CF. Journal of Cystic Fibrosis Vol 8 Supp 1 (2009) S10 - S14

5.5.2 CF-associated asthma.

Asthma is an inflammatory disorder of the airways characterised by recurrent, reversible airway obstruction. However, asthma symptoms and individual, as well as test-to-test pulmonary function variability is common in CF. Reversibility (≥12% increment in FEV^1 post bronchodilator) should be consistently demonstrated before a diagnosis of asthma is made. As many as 40% of CF patients will have varying degrees of bronchial hyper-reactivity that manifests as wheezing or coughing. The management of asthma in CF patients does not differ to standard asthma treatment guidelines. Further details are available in the SATS guidelines on asthma for children and adults (http://www.pulmonology.co.za/guidelines.htm).

Some additional points in managing CF-associated asthma or recurrent wheeze:

- **Mild or intermittent symptoms only:** use intermittent (as required) inhaled short-acting β2-agonists (e.g. salbutamol, fenoterol).
  Add an inhaled corticosteroid (ICS) if symptoms are frequent or uncontrolled.
  Consider adding a long acting β2 agonist (LABA) e.g. salmeterol, formoterol to inhaled steroid therapy if symptoms are not controlled.
  Combination therapy is preferred to separate inhalers.
- The preferred delivery device is a pressurised MDI. Dry powder inhalers (DPI) and breath actuated devices can be used in older children and adults. These should however be avoided in those with advanced lung disease who may not be able to generate enough inspiratory flow to either actuate the device or inhale sufficient particles needed for optimal lung deposition. Spacers should always be used in children up to 6 years of age, with a facemask in children less than 4.
- Nebulised corticosteroid or bronchodilator therapy should be discouraged as it is less effective and time consuming.
- Bronchodilators may cause paradoxical worsening of airway obstruction in a minority of CF patients and should be discontinued if this occurs.
- ICS and LABA should be administered only after routine chest physiotherapy, nebulised antibiotics or mucolytics.
- To date, clinical experience and research data on the anti-inflammatory effects of leukotriene receptor antagonists (LTA) in CF are limited. The addition of a LTA, anti-histamine or nasal corticosteroid is often needed in atopic patients.
- Consider and alternate diagnosis in CF patients with “uncontrolled asthma”. Specifically: allergic bronchopulmonary aspergillosis (ABPA), gastro-oesophageal reflux disease (GORD) and adverse effects of inhaled therapies like antibiotics or hypertonic saline.

5.5.3 Allergic bronchopulmonary aspergillosis (ABPA)

ABPA is a complex IgE-mediated hypersensitivity reaction that occurs in response to exposure to *Aspergillus* antigen products present in the airway. This reaction to *Aspergillus* spores leads to mucoid impaction of bronchi with inflammation and bronchial obstruction. This results in acceleration of the bronchiectasis, fibrosis and further respiratory compromise.

ABPA occurs in 2-15% of CF children but the incidence is lower in adult CF patients. The clinical picture includes fever, malaise, expectoration of brown plugs and, at times, haemoptysis; all symptoms which are difficult to distinguish from an exacerbation of CF.

The chest radiograph may show new infiltrates which may be perihilar or ‘gloved finger’ shadows due to intrabronchial mucous impaction.

ABPA is difficult to diagnose in CF patients, but identification and treatment of the disease may result in improvement in symptoms and pulmonary function. Screening for ABPA should include:

- Have high level of suspicion for ABPA in CF patients >6 years of age.
- Measure total IgE annually.

The consensus diagnostic criteria for a classic case are shown in Box 5.3:

Box 5.3 Diagnostic criteria for allergic bronchopulmonary aspergillosis in cystic fibrosis

1. Acute or subacute deterioration (cough, wheeze, shortness of breath, increased sputum and decline in exercise tolerance) not attributable to another aetiology.
2. Serum total IgE >2400ng/mL or 500 IU/mL (unless the patient is on steroids in which case the patient should be tested when off steroids).
3. Positive skin prick test to *A fumigatus* or positive RAST (Anti-IgE to *Aspergillus*).
4. One of the following:
    a. Precipitins to *Aspergillus* or IgG antibody to *A fumigatus*
    b. New or recent abnormalities on chest radiograph (infiltrates or mucus plugging) that do not clear with antibiotics and physiotherapy

Reference:
CF Foundation Consensus Conference. Clin Infect Dis Suppl 3: S225-S264, 2003

Management:

- Treatment is with oral corticosteroids. A suggested regimen is 6 weeks of tapering doses of prednisone as follows:
- First two weeks 2mg/kg/day at 0700hr (max 50mg/day);
- 2nd two weeks 1mg/kg/day at 0700hr (max 25mg/day);
- 3rd two weeks wean slowly and stop.

- Blood pressure and blood glucose should be monitored in patients on long-term or high dose corticosteroids. Diabetic patients may need to adjust insulin doses whilst on corticosteroids. Ensure adequate calcium and vitamin D supplementation to minimise the risk of osteopaenia and osteoporosis.
- The use of the anti-fungal, itraconazole has been associated with a 47% reduction in average daily steroid dose and a 55% reduction in the number of acute ABPA episodes. Voriconazole may be used. The role of anti-fungal therapy is to reduce the antigenic load and accompanying immune response. Clear evidence of this approach is however lacking.
- The monoclonal anti-IgE antibody Omalizumab (Xolair®) has been reported to be very effective treatment for severe ABPA not responsive to corticosteroids. Limited availability and high cost precludes its routine use in South Africa.

5.5.4 Haemoptysis

Haemoptysis is mostly seen in older CF patients with advanced lung disease. It may occur in as many as 60% of adolescents or adults. It usually represents an exacerbation of infection. Other factors are coughing spells, atypical lung infections including TB and clotting disorders (particularly where there is CF liver disease).

In most cases there is only a small amount of bleeding with blood flecks in the sputum. However, life-threatening bleeds (greater than 250mls/24 hrs) can occur (in 5 – 10% of adolescents and adults).

Primary treatment remains conservative with reassurance and possibly a cough suppressant e.g. codeine phosphate for the first 48 hours only. Gentle physiotherapy can be continued. Antibiotics must be given. RhDNase can safely be continued.

With large bleeds, blood transfusion may be necessary, together with fresh frozen plasma or cryoprecipitate. Pro-coagulants may be useful. Vitamin K should be administered although its benefit is not immediate. Any non-steroidal anti-inflammatory or aspirin-containing preparation must be discontinued.

In the event of larger, recurrent or unrelenting haemoptysis, bronchial artery embolisation should be undertaken in specialised centres. This should be performed sooner rather than later. As a last resort thoracotomy with ligation of the affected artery and possible lobectomy are necessary. This is associated with a poor prognosis.

5.5.5 Pneumothorax

A pneumothorax is an air leak into the pleural space secondary to rupture of a subpleural bleb, alveolus and/or air tracking via the pulmonary lymphatic and interstitial spaces. It may be associated with pneumomediastinum, surgical emphysema and more significantly, generalised interstitial emphysema.

The air leak is often confined because, in advanced CF lung disease, the lung is very stiff and may not collapse to the same degree as a healthy lung. If the air leak is under tension, there is acute collapse of the lung with a rise in the carbon dioxide level and respiratory distress. Pneumothorax may complicate severe infection, coughing or the placement of central lines. It is relatively uncommon in young children with CF. An incidence of up to 20% has been reported in adolescents and adult patients. Pneumothorax is more common in males than females, affects either side equally and is usually associated with advanced disease and marked airflow obstruction. Recurrences are common (up to 60%) on the same side or even on the other side.

Presentation is often subtle. Acute onset pleuritic pain and some respiratory distress are often evident in the absence of overt infection. A high index of suspicion should be maintained. Chest X-ray is used for confirmation.

Treatment:

- Small pneumothorax: Conservative with high FiO_2.
- If after 24-48 hours the lung is not re-expanded or if the pneumothorax is significant, intercostal tube drainage with a suitable sized drain is required.
- Chemical or limited surgical pleurodesis (with non-resolution or recurrences), keeping in mind that this procedure would be a relative contraindication to future lung transplantation.

Treatment must include step up therapy for the lung infection. The presence of an intercostal drain may exacerbate underlying chest infection if pain is not relieved. Gentle negative pressure using suction may be applied to the drain to help to expand the lung fully.

5.5.6 Antibiotic allergies and hypersensitivities.

Hypersensitivity to antibiotics can be problematic and is mainly encountered with β-lactam antibiotics. Such reactions usually take the form of skin rashes which may range from mild erythematous reactions to Stevens Johnson Syndrome. Angio-oedema and interstitial nephritis may occur and rarely anaphylaxis. When a reaction has previously occurred the offending drug should not be used but in certain circumstances where there is resistance it may be necessary to consider using that agent. Unless contraindicated because of previous Stevens Johnson Syndrome, desensitisation is safe and effective and should be attempted.

Treatment of pulmonary infections can be problematic in the face of combined drug resistance and hypersensitivity. In extreme circumstances desensitisation can be considered according to standard protocols in an intensive care unit setting (see Appendix 10).

5.5.7 Respiratory Failure and ventilation.

As the disease progresses, patients with CF become more hypoxaemic and eventually an elevation of carbon dioxide also occurs, more notably during sleep. Symptoms of early morning headache and daytime fatigue suggest respiratory failure. When this stage is reached, patients should ideally and where feasible be given the opportunity to be assessed for lung transplantation if they so wish.

Oxygen therapy

This can be prescribed for ambulatory as well as long term therapy. Assessing the need for domiciliary oxygen includes optimisation of medical therapy, blood gases (in adults) or overnight oximetry.

Long term oxygen may be prescribed in patients with CF when the PaO_2 is < 8kPa or significant de-saturations have been documented during sleep. Supplemental oxygen may also improve exercise capacity in patients who de-saturate with exercise.

Oxygen concentrators are the most practical way of providing domiciliary oxygen continuously. Flow rates are adjustable up to 5l/min. Portable cylinders with conserver devices are available for ambulatory oxygen. Oxygen concentrators and portable cylinders are available from VitalAire and Afrox.

In patients with end-stage respiratory failure who have already received maximal medical treatment, initiation of intubation and mechanical ventilation requires careful consideration as this may only prolong the process of dying. However, it can tide a patient over an acute exacerbation. In centres where transplantation is feasible, ventilation may allow for sufficient time to enable patients to receive lung transplants. In this setting, non-invasive ventilation techniques using nasal intermittent positive pressure ventilation (NIPPV) may be effective. This technique allows the patient to eat, talk and communicate. NIPPV may also be useful in the longer term for patients with chronic respiratory failure at home. The goals of non-invasive ventilation are presented in the box below

Reference:
Melitas S, Hill NS. Noninvasive Ventilation. Am J Respir Crit Care Med 2001; 163:540-577

Hodson ME, Madden BP, Steven MH, Tsang VT, Yacoub MH. Non-invasive mechanical ventilation for cystic fibrosis patients - a potential bridge to transplantation. Eur Respir J 1991; 4:524-527

5.5.8 Lung transplantation

Transplantation remains the best option for prolonging life for many patients with CF who are nearing death. In South Africa, transplantation for CF is in its infancy and

Short-term	**Long-term**
Relieve symptoms	Improve sleep duration and quality
Reduce work of breathing	Maximise quality of life
Improve or stabilise gas exchange	Enhance functional status
Optimise patient contact	Prolong survival
Good patient-ventilator synchrony	
Minimise risk	

limited facilities exist. This is compounded by the universal problem of a shortage of donor organs. Bilateral sequential cadaver lung transplantation is the usual procedure of choice with survival rates in established centres at 1 year of between 70 and 80%. Currently international figures suggest a 50% chance of survival at 10 years post transplant. Lung transplantation in South Africa is currently only available to patients with private medical insurance and only at Milpark Netcare Hospital in Johannesburg.

There are now several patients from centres abroad who have survived more than 10 years after transplantation. Progress is also being made with living-donor lobar transplantation. Appropriate selection and referral is essential in order to try and achieve the most favourable outcome. Basic selection criteria for lung transplantation appear below.

Indications for bilateral sequential lung transplant in CF

- FEV_1 ≤30% of expected despite optimal medical therapy
- Significantly impaired quality of life secondary to chronic respiratory failure despite optimal medical management
- FEV_1 >30% of expected but recurrent, frequent acute pulmonary exacerbations requiring prolonged and frequent intravenous antibiotics and admission to hospital despite optimal medical management and compliance that results in a significantly impaired quality of life.

- Rapid decline in lung function, especially in young female CF patients, who have a particularly poor prognosis.
- Massive haemoptysis not responding to embolisation.
- Hypoxaemia (PaO_2<55mm Hg) or hypercapnia ($PaCO_2$>50mm Hg) measured from resting arterial blood gases obtained while the patient is breathing room air, are useful criteria and are associated with a prognosis of <50% survival in two years. However, patients should be considered candidates for transplant if they meet FEV_1 criteria even though they may not yet be markedly hypercapnic or hypoxemic
- Patient should actively want transplantation
- Recurrent ICU admissions for ventilation

Non-infectious contraindications to transplantation

- ≥60 years of age
- BMI <18.5kg/m^2 or 130% < Ideal Body Weight <70%
- co-morbid dysfunction of major organs other than the lung, particularly
- renal dysfunction with a creatinine clearance of <50mg/ml/min
- severe/end-stage CF related liver disease should be an absolute contraindication unless concurrent liver transplant is possible
- poorly controlled diabetes with end-organ damage
- invasive ventilation at the time of transplantation
- osteoporosis
- chronic corticosteroid requirements > 20mg/day of prednisolone or prednisone
- active malignancy within the past two years (extra capsular renal tumours, breast cancer ≥ stage 2, colon cancer > Dukes A and malignant melanoma ≥ level 3 should have a waiting period of 5 years before transplantation)
- significant left ventricular dysfunction
- immobility
- severe musculoskeletal disease affecting the thorax, e.g. kyphoscoliosis
- progressive neuromuscular disease

Infectious contraindications to transplantation

- Absolute
  - Infection with HIV
  - Hepatitis B antigen positivity.
  - Hepatitis C with biopsy-proven histologic evidence of liver disease
  - Active invasive *Aspergillus* or TB
- Relative
  - Pan resistant colonising organisms

- Colonisation with *Burkholderia cepacia* (especially *cenocepacia* or Genomovar III)

Psychological contraindications to transplantation

- noncompliance with medical care or treatment plans
- psychiatric illness precluding compliance
- substance use or addiction in the last 6 months e.g. alcohol, tobacco, narcotics
- psychosocial problems that cannot be resolved and that have a high likelihood of impacting negatively on the patient's outcome e.g. lack of social support

Colonisation with fungi or atypical mycobacteria is not an absolute contraindication to transplantation. Cases should be considered on an individual basis. Adequately treated *M tuberculosis* is not a contraindication to lung transplantation. Patients receiving non-invasive ventilatory support who meet all other criteria are eligible for lung transplantation. Patients who do not currently qualify for transplantation but may ultimately meet the criteria for lung transplantation should not have referral delayed while undergoing corrective treatment. Early referral for transplant assessment is essential.

This section should be read in conjunction with Section 11.7 on Palliative Care in CF (Page *)

6. NUTRITION

The secretion of digestive juice from the pancreas is severely reduced in most CF patients from an early age and, unless treated with pancreatic enzyme supplements, the digestion and absorption of food are severely impaired. Inadequate absorption of food from the bowel will lead to unpleasant digestive symptoms, malnutrition, poor growth and specific deficiencies of fat soluble vitamins A, D, E and K.

Well-nourished patients have fewer infections, better quality of life and increased life span. It is, therefore, essential that CF patients be referred to a dietician experienced in the management of CF. Every effort must be made to achieve normal growth in CF as good nutrition promotes good quality of life and longevity.

6.1 FEEDING OF INFANTS

Most infants with CF will thrive on breast milk (or a standard infant milk formula if breast feeding is problematic). A predigested medium chain triglyceride fat containing formula may be beneficial for infants who have undergone bowel resection for meconium ileus or those who have co-existing cow milk intolerance (see Appendix 9). If the infant is breast fed and thriving, this method of feeding should be encouraged. Bottle fed infants may require up to 200ml/kg body weight/day. Nutritional outcome is no better when babies are formula fed.

If the infant is failing to thrive despite adequate pancreatic enzyme supplements and an adequate oral intake, additional energy supplements are added to the milk. Early weaning is not usually necessary. Some babies may require sodium supplementation (see Section 6.4.1, p*).

6.2 PANCREATIC ENZYME SUPPLEMENTATION

Virtually all CF patients (95%) require pancreatic enzyme supplementation owing to inadequate pancreatic secretion. A number of preparations are available. Higher doses than those recommended in the manufacturers' literature are usually required. The acid-resistant microsphere preparations are significantly more effective than the older pancreatic enzyme preparations which should NOT be used for CF patients.

High Lipase Pancreatic Preparations

Pancreatic preparations containing three to five times the quantity of lipase (Creon 25000®) are available for older children. Care should be taken to avoid total daily lipase intake of greater than 10000 U/kg/day.

6.2.1 General guidelines on use of pancreatic enzyme supplements

1. **Type** Use one of the acid-resistant microsphere preparations.
2. **Time** Enzymes are best given at the beginning or early in the meal. Half the dose at the beginning and half in the middle of the meal is recommended.
3. **Method** Capsules should be swallowed whole from as early an age as possible. If removed from the capsule, the microspheres should *not* be sprinkled on or mixed with the whole meal. Microspheres should be mixed with a little fluid and taken in one swallow. If mixed with food or fruit puree, they should be mixed with one teaspoonful and taken in one or two swallows. Microspheres must not be chewed.
4. **Dose** Enzymes are required with all meals and drinks that contain fat.

   Start with ⅓ or ½ capsule (i.e. 3000 to 5000 units) in infants and one or two capsules per meal in older patients. Increase gradually until the bowel symptoms are controlled.

   Increase the dose with more fatty meals. It is advisable not to exceed a dose of 3000 units of lipase/kg body weight/meal or 10 000 units of lipase/kg body weight/day. Some patients may require higher doses.

   Changes in dose should be made gradually to avoid constipation.

   Insufficient pancreatic enzyme will cause symptoms of malabsorption e.g. abdominal pain, pale, loose, fatty, offensive stools, and will eventually lead to growth failure.

Patients who require larger doses than recommended may warrant the addition of an H_2 blocker or proton pump inhibitor to reduce gastric acid secretion. This may permit a reduction in the number of capsules required.

6.3 NUTRITIONAL MANAGEMENT

Most individuals who have CF have higher than normal energy requirements due to incompletely controlled intestinal malabsorption, increased energy expenditure, chest infections and physical therapy.

A diet that is high in both energy and protein is required to achieve normal weight gain and growth. Individual requirements vary but most patients need 20 to 80% more energy than an unaffected individual of the same age. The food intake of most patients does not meet this increased energy requirement.

Patients are encouraged to take foods rich in energy such as fried foods, crisps and chocolate and those rich in protein such as milk, cheese and meat as part of their total balanced diet. Dietary sources of fat such as butter, margarine, cream or mayonnaise can be added to food to increase the energy density.

Dietary fat intake should never be restricted as this nutrient is essential to achieve a high energy intake and a normal nutritional state with growth. If foods with a high fat content cause abdominal pain or more frequent and paler stools, the dose of pancreatic enzymes should be increased whenever that food is taken. The dose is gradually increased until the food is tolerated and the steatorrhoea resolves.

It is very important that children are given frequent meals and snacks (5-6 per day) from a young age to maximise daily energy intake. Toddlers should get into the habit of regular eating. This habit will stand them in good stead as they grow up.

Psychological factors may play a major role in poor food intake patterns in some children and adolescents.

A booklet by Dr. Tony Westwood of the Red Cross Children's Hospital in Cape Town provides useful recipes and advice on CF nutrition (available from SACFA or CF centres).

6.4 DIETARY SUPPLEMENTS

If the patient's weight gain is inadequate or the appetite poor, dietary energy supplements can improve energy intake. See Appendix 9 for a list of available products and their use. The type and amount of supplement recommended depends on the patient's age, preference and requirements and should be prescribed on an individual basis. The supplements should be taken in addition to normal food to increase the total daily energy intake. They should not replace a meal. They should be given with a snack between meals or as a drink after meals.

6.4.1 Salt

There is excessive loss of salt in sweat in CF. Most South African diets contain sufficient salt to compensate for this. There are two circumstances under which excess salt loss may cause clinical problems for someone with CF.

All infants with CF lose about 0.5 mmol/kg more sodium than non-CF infants. Salt deficiency can contribute to poor weight gain and must be sought where other explanations (e.g. inadequate pancreatic supplementation) are not present. Hyponatraemic dehydration may be a presenting feature of CF. In these circumstances, 0.5-1mmol/kg of salt per day in a 3% solution should be given until the age when solids constitute most of the child's diet.

Older children who live in and all who exercise in conditions of high environmental temperature should take salt tablets (1-3 per day) or increase their dietary salt and also increase their fluid intake.

Salt intake should not be restricted but excessive salt intake is dangerous.

6.4.2 Vitamins

All CF individuals should receive supplements of the fat soluble vitamins A, D and E. The recommended daily supplements that usually achieve normal plasma levels are considerably greater than the usual daily recommended intake. The plasma fat soluble vitamin levels should be checked annually and the dose adjusted depending on the levels. Dosages are given in Appendix 8.

Vitamin A
Vitamin A deficiency may cause night blindness in older patients. Clinical progress improves when low levels of vitamin A detected at assessment are corrected.

Vitamin D
Vitamin D deficiency may cause rickets (which is rare) and osteomalacia. Osteoporosis and low levels of vitamin D metabolites are well documented, particularly in older patients.

Vitamin E
Vitamin E deficiency may cause haemolytic anaemia in infants. In older CF individuals Vitamin E deficiency may cause neurological problems. Vitamin E appears to be important as an anti-oxidant in CF.

Vitamin K
Vitamin K may be low, particularly if there is an associated liver problem, and supplements of Vitamin K, 10mg daily, may be required if the INR is abnormal or if elective surgery is planned. Vitamin K is also important in bone disease.

6.4.3 Minerals

Iron
Iron supplements are not routinely needed. Full blood count should be monitored annually. Patients with moderate to severe lung disease require iron supplementation.

Calcium
Many CF patients take insufficient dietary calcium. Calcium supplementation is recommended to maximise bone mineral accretion.

Zinc

If the child is malnourished at the time of diagnosis, zinc acetate should be given for a month at a dose of 10mg daily for infants and 20mg a day for those over this age.

6.4.4 Assessment of Growth and Nutritional status

Growth and nutritional status need to be assessed at a specialised CF clinic every 1 to 3 months

Weight, length/height and head circumference
These must be measured and plotted on growth charts at regular intervals, looking at the pattern of growth. Current standards used in South Africa are the WHO *z*-score charts of weight and length/height for age and weight for height. Body mass index (BMI) is a useful index and plotted on WHO charts for children and standard tables for adults. Children under 5 years of age should have their head circumference measured every 6 months.

Mid arm muscle circumference and triceps skinfold thickness are useful indicators of lean body mass and body fat.

Growth velocity is an important measure and can assist in identifying sub-optimal growth.

Dietary Assessment
Many CF patients do not eat enough. Dietary intakes must be assessed regularly to ensure that energy requirements are being met. As part of their annual assessment, patients should record a 3-day dietary diary from which their nutritional intake is analysed and advice is given accordingly.

6.5 NASOGASTRIC AND ENTEROSTOMY FEEDS

Supplemental tube feeds are frequently useful in patients with severe lung involvement. Before embarking on these forms of feeding the diet must be optimised, pancreatic enzyme replacement therapy has to be maximised and H_2 blockers/protein pump inhibitors have been introduced.

Indications:

- Children less than 5 years: weight/height less than 85% expected; weight loss or plateau in weight gain over 4 months.
- Children 5-18 years: weight/height <85% expected; weight loss or plateau in weight gain over 6 months
- Adults: a BMI of <19; weight loss of >5% body weight for more than 2 months duration

Methods:

- Fine nasogastric tube left in permanently or replaced every morning (not usually well tolerated in the long term).
- Gastrostomy:
- Percutaneous endoscopic gastrostomy (PEG) with gastrostomy button.
- Traditional surgical placement.

Technique:

- Feed for 10-12 hours at night (stop 2 hours before morning physiotherapy session).
- Eat normally during the day. At least 40-50% of the total daily energy requirement should be given at night.
- Ideally use a peristaltic pump to avoid the tube blocking.
- Use Ensure® as food source (not semi-elemental expensive preparations).
- Take two thirds of enzymes at beginning and one third in morning on wakening or half on starting and half on going to sleep. Dosage to be adjusted according to usual enzyme requirement per gram of fat for the patient.
- Patients tolerate smaller volumes of higher concentration feeds (1 or 1.5kcal/ml) better than larger volumes of less concentrated formulae.
- Prokinetic agents may be required. Patients should be encouraged to sleep with the head elevated (30%).

Dangers:

- Vomiting, aspiration and increase in gastro-oesophageal reflux.
- Hyperglycaemia. Baseline oral GTT should be done before this type of feeding is commenced. Some patients will require insulin supplementation during feeding at night (see Diabetes mellitus Chapter 8 page *)
- Leakage, bleeding or ulceration at the gastrostomy site.

7. GASTROINTESTINAL PROBLEMS

7.1 ABDOMINAL PAIN AND PERSISTING BOWEL SYMPTOMS

Abdominal symptoms in CF may be acute, chronic, recurrent or obstructive. Ongoing bowel symptoms have many causes, making accurate diagnosis difficult at times. They may be due to

- constipation/faecal loading,
- the distal intestinal obstruction syndrome (DIOS - a situation specific to CF),
- intussusception,
- malrotation,
- giardiasis,
- gallstones,
- appendicitis,
- colonic stricture,
- pseudomembranous colitis, or
- inflammatory bowel disease.

Children who had surgery for meconium ileus may develop adhesive intestinal obstruction.

7.1.1 Distal intestinal obstruction syndrome (DIOS)

Contributory factors:

- Poor adherence to and/or insufficient pancreatic enzyme supplementation.
- Insufficient fluid and water intake.
- Low fibre intake.

In DIOS there is an accumulation of the products of maldigestion mainly in the ileum and the right side of the large colon. The clinical effect is to produce colicky abdominal pain associated in many but not all cases with symptoms (vomiting, constipation) and signs (abdominal distension) of intestinal obstruction. Anorexia may also be a consequence. Often a right lower quadrant abdominal mass is felt. Faecal masses may also be felt elsewhere in the abdomen.

Management:

- Optimise diet, enzymes, fluid and fibre intake.
- X-ray abdomen to determine degree of faecal loading.
- Clear the bowel with: a) Gastrografin® mixed with fruit juice; or b) balanced electrolyte polyethylene glycol solution (Pegicol®, Kleen-Prep®, Golytely®). Gastrografin® is the preparation of choice in severe cases. N-acetyl cysteine (Parvolex®) may be added by mouth.
- If acutely obstructed admit, keep nil per mouth (NPM), improve hydration and use Gastrografin®, Kleen-Prep®, Pegicol® or Golytely®. If the obstruction persists, surgery may be required (uncommon).

Faecal loading is a risk in CF. Increased fibre and fluid intake from an early age should reduce the chances of this and DIOS occurring.

7.1.2 Hyperacidity/Dyspepsia

Hyperacidity (with decreased bicarbonate secretions) with epigastric pain may respond to the introduction of an H_2 receptor blocker or proton pump inhibitors.

7.2 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

The incidence of GORD is significantly increased in CF patients of all ages. Factors playing a role are lower airway obstruction with flattening of the diaphragm, increased negative intra-thoracic pressure with inspiration, increased intra-abdominal positive pressure during coughing and also delayed gastric emptying.

As the signs and symptoms of GORD are perfectly mimicked by the traditional symptoms of CF, making a definitive diagnosis is difficult. GORD should be considered in any CF patient who, despite compliance with CF therapy, continues to have problems with progressive pulmonary disease, vomiting, abdominal pain or failure to thrive. A high index of awareness is essential.

Investigations may include a barium swallow which gives good structural differentiation but the presence or absence of GOR may be over called or missed. Milk scans (scintigraphy) are more physiological and more informative but are only available at a few of the big centres. The same applies to oesophageal pH monitoring. If complications of severe oesophagitis such as stricture or bleeding are suspected, endoscopy is the definitive diagnostic test.

Posture, head of bed elevation and thickened feeds have little effect on GORD. There are no pro-kinetic agents available that do not have medico-legal implications. The use of Cisapride must be limited to children with a normal ECG and who are not on medications such as azithromycin or anti- fungals. Acid suppression with omeprazole remains the most effective therapeutic option. Current experience with long term use of omeprazole in young children has revealed few problems but the potential increase in infections remains a worry. Surgical intervention with a Nissen fundoplication has a much greater failure rate and breakdown in CF patients, most likely due to the recurrent stresses of coughing, but should be considered in severe case and when PEG feeding is being considered.

7.3 LIVER DISEASE

Significant liver disease occurs in about 10% of people with CF. A larger proportion (27-35%) have abnormalities of liver function or other evidence of liver involvement. An increased incidence of gallstones and cholecystitis is noted in older CF patients.

Severe liver disease has a negative effect on lung health in CF and therefore liver involvement must be sought. Liver function tests should be done annually on all CF patients. If these are abnormal or if the liver is palpable, an ultrasound test is required. Early liver disease requires treatment with bile acids as these seems to slow progression of CF-related liver disease (see below).

Of the 10% of patients with significant liver disease, a large proportion will have hepatic cirrhosis with portal hypertension. Severe liver failure is uncommon. Most problems are associated with portal hypertension (bleeding varices, hypersplenism etc.).

Diagnosis is made based on clinical features such as a palpable liver, abnormal liver function tests (part of the annual review tests. See page *), or ultrasound features. It is important to consider causes of liver disease not directly related to CF such as drug toxicity and infections.

Management:

- All patients with persistently abnormal liver function tests or early liver disease on ultrasound scanning should receive ursodeoxycholic acid (20mg/kg/day) in 2 or 3 divided doses. This is now part of routine care for CF-related liver disease worldwide.
- Fat-soluble vitamin supplementation is required (see dosages in Appendix 8)
- Annual liver function and ultrasound are recommended for those with early liver disease
- Bleeding oesophageal varices should be sclerosed endoscopically or banded when appropriate.
- Liver transplant may be indicated in a few cases.

Reference:

Colombo C. Liver disease in cystic fibrosis. Curr Opin Pulmonol 2007:13:529-536

8. IMPAIRED GLUCOSE TOLERANCE AND CYSTIC FIBROSIS-RELATED DIABETES MELLITUS

8.1 Management of cystic fibrosis-related diabetes in children and adolescents

There are important differences between CFRD and both type I and type 2 diabetes, which necessitate a unique approach to diagnosis and management (Table 1) and the involvement of a paediatric endocrinologist as part of the management team. Few CF patients have completely normal blood glucose levels at all times. The earliest change is variable, intermittent post-prandial hyperglycemia followed by impaired glucose tolerance (IGT), then diabetes without fasting hyperglycemia, and diabetes with fasting hyperglycemia. A diagnosis of ‘‘normal’’ glucose tolerance on oral glucose tolerance testing does not exclude abnormal post-prandial glucose levels at home - when far more than 75 grams of carbohydrate may be consumed.

Factors specific to CF that cause fluctuations in glucose metabolism include:

- respiratory infection and inflammation,
- increased energy expenditure,
- malnutrition, glucagon deficiency and
- gastrointestinal abnormalities
  - malabsorption,
  - altered gastric emptying and intestinal motility
  - liver disease.

Table 8.1. A comparison of type 1 diabetes, type 2 diabetes and CFRD

	Type 1 diabetes	Type 2 diabetes	CFRD
Onset	Acute	Insidious	Insidious
Peak age of onset	Children & adolescents	Adults	18-24years
Antibody+	Yes	No	Probably No
Insulin secretion	Eventually absent	Decreased	Severely decreased but not absent
Insulin sensitivity	Somewhat decreased	Severely decreased	Somewhat decreased
Treatment	Insulin	Diet, oral medication, insulin	Insulin
Microvascular Complications	Yes	Yes	Yes but less
Macrovascular Complications	Yes	Yes	No
Cause of death	Cardiovascular disease Nephropathy	Cardiovascular disease	Pulmonary disease

Pathophysiology

Abnormal chloride channel function in CF results in thick viscous secretions causing obstructive damage to the exocrine pancreas with progressive fibrosis and fatty infiltration. This result in disruption and destruction of islet architecture leading to

loss of endocrine beta, alpha and pancreatic polypeptide cells. Beta-cell dysfunction is not related to autoimmune disease in CF, outside of isolated case reports of autoantibody positive individuals with CFRD.

The role of insulin deficiency

The primary defect in CFRD is severe but not absolute insulin deficiency. Virtually all exocrine insufficient patients with CF, with and without diabetes, show evidence of beta-cell dysfunction . Fasting insulin and C-peptide concentrations are normal, but there is delay and blunting of peak insulin secretion during a standard OGTT. This effect is more pronounced with worsening glycemic status. Delayed insulin secretion during the OGTT is related to loss of first phase insulin secretion, which is found even in CF patients with normal glucose tolerance. Secretion of other islet hormones is also impaired in CF, in particular loss of glucagon responses.

The role of insulin resistance

In CF patients without diabetes, insulin sensitivity is variable. While most of these patients are sensitive to insulin in their baseline state of health, infection and inflammation increase insulin resistance. CF patients with diabetes are insulin resistant, due to both decreased peripheral glucose uptake and poor insulin suppression of hepatic glucose production. Insulin resistance can become acutely severe during infectious exacerbations.

8.2 Clinical Features:

- Unexplained polyuria or polydipsia
- Failure to gain or maintain weight despite nutritional intervention
- Poor growth velocity
- Delayed progression of puberty
- Unexplained chronic decline in pulmonary function

8.3 Diagnosis of CFRD

- Oral glucose tolerance test
- Random and fasting glucose levels - while hyperglycemia is diagnostic for diabetes, normal fasting or random glucose levels do not exclude a diagnosis of diabetes in CF
- Continuous glucose monitoring - this may aid the diagnosis of CFRD when considered in conjunction with the OGTT result and the clinical scenario.
- HbA1c has been shown to be unreliable in the diagnosis of CFRD.

8.4 Treatment

8.4.1 Insulin Therapy

Insulin is the only recommended medical therapy for CFRD. Insulin therapy may help to stabilise lung function and improves nutritional status in patients with CFRD. There are no definitive data to date on the benefits of insulin therapy for CF children and adolescents with milder forms of abnormal glucose tolerance, although a small case series has demonstrated similar benefit. Choice of the insulin regimen

depends on individual needs and characteristics of the patient. The standard basal bolus regimen provides background insulin and a continuous anabolic effect. The short acting insulin controls postprandial hyperglycaemic episodes and provides flexibility for variable eating patterns. Alternatively, effective basal-bolus therapy can be accomplished with insulin pump therapy.

8.4.2 Oral diabetes agents

Oral diabetes agents are currently not recommended in CFRD.

8.4.3 CFRD without fasting hyperglycemia and CF with impaired glucose tolerance

While insulin treatment of CFRD with fasting hyperglycemia has been the accepted standard-of-care for several years, treatment of less severe glucose tolerance abnormalities has been more controversial. Results from a recent multi-center, randomized, placebo-controlled clinical trial demonstrate that premeal insulin therapy reversed chronic weight loss in adults with CFRD without fasting hyperglycemia and this effect was sustained over one year of treatment. Thus, insulin therapy is now recommended for all patients with CFRD with or without fasting hyperglycemia. There are insufficient data at present to make recommendations for patients with IGT or those who have NGT by OGTT testing but intermittent asymptomatic hyperglycemia when tested at home.

Table 8.2 Differences in the dietary management of type 1 and type 2 diabetes versus CF related diabetes (CFRD)

	Type 1 & Type 2 diabetes	CFRD
Calories	<100% of normal for age and gender – often have to watch or restrict calories to prevent overweight	Usually require120-150% (or more) of normal caloric intake for age and gender to prevent underweight
Fat	30-35% of total energy	40% of total energy
Refined Sugars	Up to 10% of total energy	No Restriction
Carbohydrate	50-55% total energy	45-50% of total energy
Dietary fibre	Encouraged due to beneficial effects (Age in years + 5g per day)	Encouraged in the well nourished, but in poorly nourished patients, it may compromise energy intake
Protein	10-15% of total energy; not>1g per kg body weight	200% of reference nutrient intake
Salt	Low intake < 6g /day	Increased requirement - unrestricted intake

Routine annual testing for diabetes should be performed in CF patients aged 10 years and older during a time when they are clinically well. The decision to treat should be based on consideration of blood glucose levels and the impact of treatment on the individual's overall condition.

9. CYSTIC FIBROSIS RELATED BONE DISEASE (CFRBD)

9.1 DECREASED BONE DENSITY

Cystic fibrosis (CF) is a multi-system disease. Its related bone disease (CFRBD) is manifested clinically with:

- decreased bone density
- pathological fractures
- kyphosis

CFRBD is more likely in patients with:

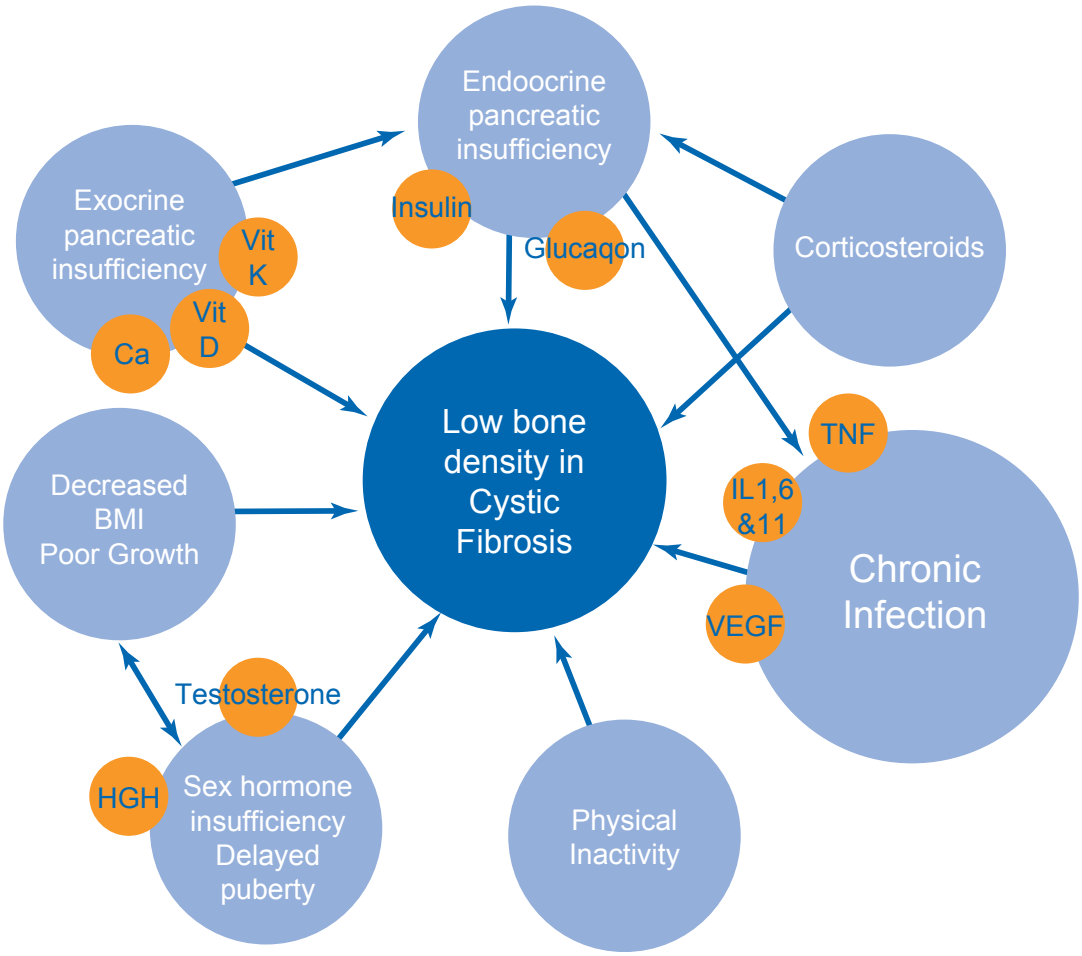
- malnutrition (low BMI, Vitamin D, K and calcium deficiency)
- significant lung disease on the basis of chronic pulmonary infection

Late childhood and adolescence are critical periods when bone accrual during skeletal formative period is most rapid.

It is essential that an attempt be made to prevent CFRBD and, failing this, that it is recognised early and treated appropriately.

The **causes of low bone density** in CF are shown in Figure 9.1:

Figure 9.1 Contributors to low bone density in CF



9.1.1 Early recognition of reduced bone density

Reduced bone density should be measured by using Dual energy X-ray absorptiometry (DxA scan). This should commence in CF patients from the age of 16 years or as early as 8 years in children who have <90% ideal body weight, FEV_1 <50% of predicted, glucocorticosteroid use of ≥ 5mg/day for ≥ 90 days / year, who have delayed puberty, a history of pathological fractures or who have been transplanted or are being assessed for transplantation.

9.1.2 Interpretation of the DxA scan

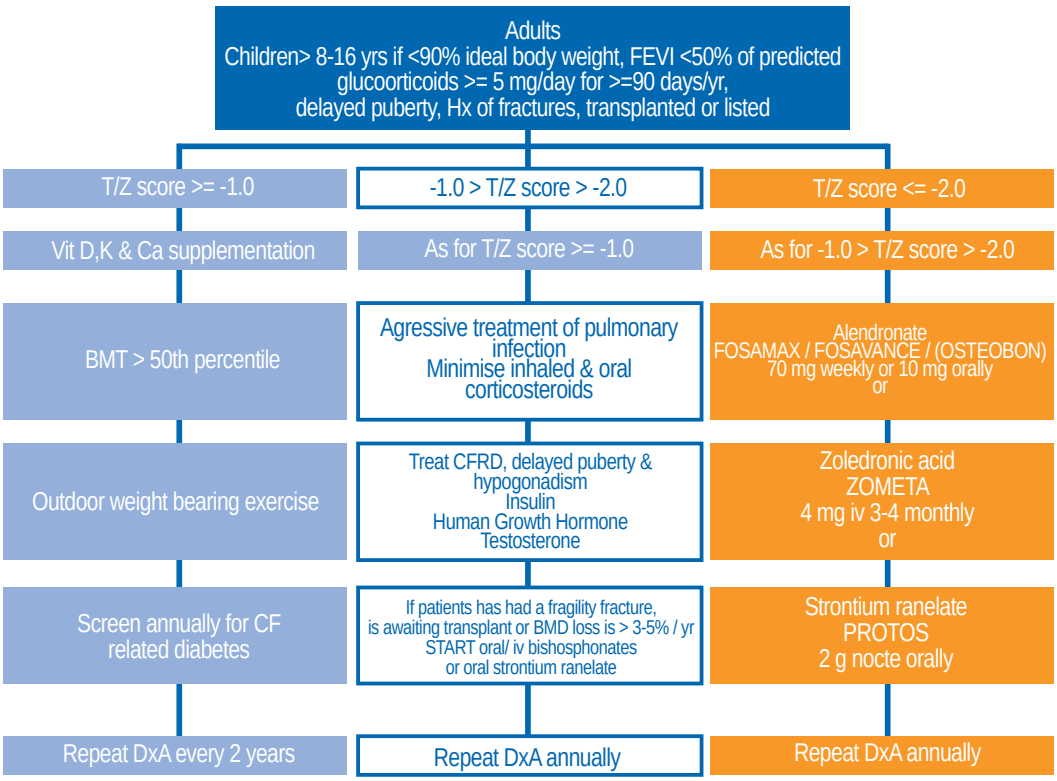
The DxA scan should be interpreted with care in children or young adults whose growth plates have not fused. The DxA scan must be corrected for delayed skeletal maturation by assessing bone age before interpreting the DxA scan. *Z*-score are used when growth plates have not yet fused and thereafter T scores are referred to. In CF, unlike in post-menopausal women:

- T/Z score ≥ -1 is normal
- -1 >T/Z score > -2 is considered "osteopaenic"
- T/Z score ≤ -2 is considered to be "osteoporotic"

9.1.3 Management of bone mineral density abnormalities

Figure 9.2 shows the treatment recommended according to severity of bone disease.

Figure 9.2 Treatment modalities for bone mineral loss in CF



9.2 BONE AND JOINT PAIN IN CYSTIC FIBROSIS

Cystic Fibrosis Associated Arthritis (CFAA) and Hypertrophic Pulmonary Osteoarthropathy (HPOA) in CF are relatively common, have similar presentations but require different management.

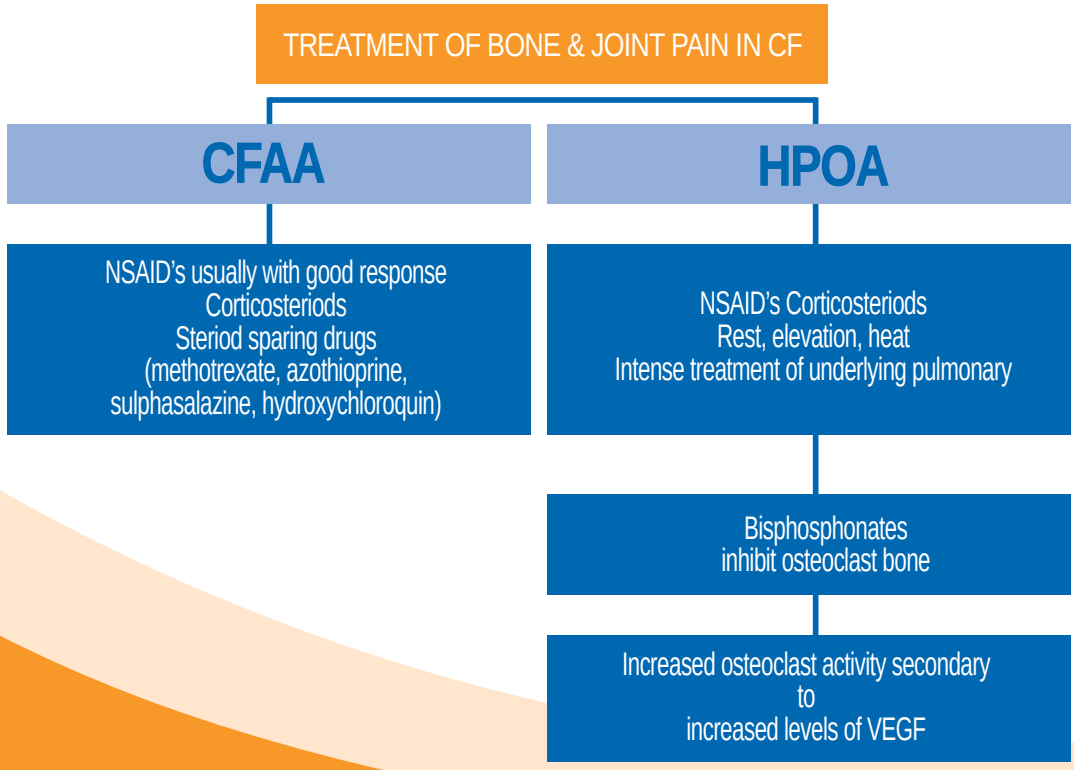
9.2.1 Cystic Fibrosis Associated Arthritis (CFAA)

This commonly presents with pain in the large joints like the knee, ankle, shoulder, elbow and wrist. The pain is episodic and usually last for less than a week. The arthritis is non erosive, onset of pain is sudden and can often be disabling and can have an associated fever and skin rash. It can be associated with an acute pulmonary exacerbation and associated hyperactive immune response. There are no X-ray changes. CFAA is not more common in patients with severe lung disease. Treatment – see Figure 9.3

9.2.2 Hypertrophic Pulmonary Osteoarthropathy (HPOA)

HPOA presents with symmetrical joint pain usually involving the knees, ankles and wrists. Onset is more insidious, pain is initially mild and the joint is swollen, tender and warm often resembling cellulites. X-ray of the involved joint may show periosteal elevation with new bone formation along long bones. A radio nucleotide bone scan shows diffuse, intense and symmetrical uptake. HPOA is more common in patients with severe lung disease. Treatment – see Figure 9.3

Figure 9.3 Treatment of bone and joint pain in CF



10. GENITO-URINARY AND RELATED PROBLEMS

10.1 FERTILITY AND PREGNANCY

Men who have CF are usually infertile. This should be confirmed after puberty using sperm analysis. Although sperm is produced in the testes and sexual drive and performance are normal, there is blockage or absence of the vas deferens preventing the sperm travelling from the testis to the penis. In certain centres it is now possible to use sperm aspirated from the testes of men with CF for *in vitro* fertilisation.

Although women with CF may have diminished fertility, they can conceive normally. If a woman with CF intends becoming pregnant, this should be discussed with a CF physician. Those with advanced lung disease (^{FEV1} <1,6l) should be advised against pregnancy. In cases where the lung function is satisfactory, genetic counselling should be offered. If the partner is a CF carrier the chance of offspring being affected is 1 in 2. Prospective partners should be screened for carrier status. (Refer to Section 3, p11).

Pregnancy and lactation exert a nutritional strain on the mother and the nutrition of every mother who has CF should be augmented according to her clinical condition and circumstances. Successful breast feeding in mothers who have CF is possible.

Women with CF can use any of the methods of contraception available. It should however be discussed with a doctor. Men with CF should not assume that they are infertile. Safe sex should be practised to avoid unintended pregnancy and sexually transmitted infections.

Reference:
Michel SH, Mueller DH. Impact of lactation on women with cystic fibrosis and their infants: a review of five cases. J Am Diet Assoc. 1994;94(2):159-165

10.2 URINARY INCONTINENCE

Urinary incontinence (UI) is common in the female CF population and onset has been reported as young as 9 – 11 years. Some males also show mild symptoms of urinary incontinence.

Coughing, forced expiratory techniques, sneezing and laughing are the main causes of UI, and this affects both airway clearance and daily life. It is necessary to ask the patient about UI as most people are too embarrassed to mention the problem. As the occurrence and severity of UI increases as the disease progresses, it is important to teach pelvic floor exercises and controlled coughing to all pre-pubertal girls, and where necessary to include electrical stimulation, bio-feedback and bladder training.

11. PSYCHOSOCIAL ISSUES

11.1 PARENTING

It is not surprising that a serious life-long disease such as CF requiring daily treatment, frequent hospital attendance and admission to hospital should be associated with considerable emotional stress for the patient and family. Marital strain is likely and parents need to make time for each other. The parents' emotional health impacts on the child's health. Most patients and families cope reasonably well but may need help in anticipation of and at crucial times such as at diagnosis, starting school, admission to hospital, adolescence, deteriorating health or bereavement. Disciplining of the child with CF should be no different from family norms. Agreement between parents on limit setting is necessary. Overindulgence is a risk. Siblings without CF should not be neglected.

All professionals in contact with the family should be aware of the emotional consequences of CF and aim to assist the family particularly at times of heightened difficulty. Regular discussion of issues is necessary. Most CF units have specialised social workers who can help relieve stress and enable families to cope more effectively by providing a range of services. These include counselling and emotional support.

11.2 PATIENT ADHERENCE TO THERAPY

CF is a complex disease requiring a significant number of treatments each day. It is also a chronic disease, requiring these treatments for life. These two factors significantly impact on adherence to regular therapy. Since adherence is the fundamental therapeutic step, every attempt should be made to ensure and facilitate patient and family adherence.

Some of the measures that have been shown to work include

- Written treatment plans
- Reward charts
- Adherence counselling by a staff member
- Time set aside during the medical consultation to talk about adherence
- Creative use of team members
- Involvement of family members

The important issues that need to be stressed are

- Adequate nutrition and diet
- Chest care including physiotherapy
- Psychosocial issues

11.3 TRANSFER FROM PAEDIATRIC TO THE ADULT CLINIC - TRANSITION

Patients should be prepared early for eventual transfer to an adult clinic at around the age of sixteen years. This transition requires close liaison between the paediatric team and the adult caregivers. Ideally transition should be gradual. There is good evidence that meeting the adult team before transfer aids smooth transition. Consideration should be given to establishing a transition clinic involving

paediatric and adult professionals. The needs of parents should not be forgotten, but independence of the patient needs to be encouraged.

11.4 PAIN MANAGEMENT

Pain is common in CF both due to procedures and complications of the disease. Pain relief is an essential part of CF care. Its management is discussed in the following sections:

DIOS Section 7.1.1, p

Skeletal pain Section 9.2, p

Terminal care Section 11.7, p

11.5 DEPRESSION

Many patients with CF will experience transient or protracted depression during their lifetime. Ongoing encouragement and skilled management from the CF care team is essential. This may include the services of psychologists, psychiatrists, social workers as well as a chaplain or religious advisor.

It is vital that caregivers bear the possibility of underlying depression in mind, as in addition to supportive and counselling measures, the introduction of antidepressant therapy may substantially improve the quality of patients' lives.

11.6 LIFESTYLE CHOICES

As the child reaches adolescence, and then adulthood, important life decisions need to be made in the short and long term. These relate to future educational and career choices, suitability of partners and fertility issues. Open discussions surrounding these issues should occur between patient and health professionals. Factors affecting these choices would be the state of health of individual patients, fitness, frequency and severity of pulmonary exacerbation, and the ability to live independently.

11.6.1 Career choices

No field should be totally closed to the patient, but consideration should be given to the amount and intensity of manual work, cleanliness in the work environment, exposure to extremes of temperature, dust, smoke or fumes, and the ability of the patient to cope with the lifestyle demanded of his/her chosen profession.

Potential employers need to be informed and understand the chronic nature of the condition so that work absenteeism for appointments or during acute exacerbation of illness will be tolerated.

Severely ill patients should be encouraged to apply for disability grants.

11.6.2 Sexuality

It has been noted that adolescents with CF tend to date later, date less often, feel less attractive, and have a reduced sexual desire than non affected or less severely affected individuals. Sexual issues including sexually transmitted infections need to be discussed and a balanced approach to sexual issues encouraged. Although male sterility is usual, sexual function is normal. Because sterility is not always present, unprotected sex should be avoided. In females fertility is frequently normal. Contraception needs to be discussed (see Section 10.1, p).

CF adults need to consider the chance of premature parental death should they decide to have children. They also need to give consideration to the maternal and fetal health during the pregnancy.

11.7 PALLIATIVE CARE (including End-of-life care)

Almost all deaths from CF are related to respiratory disease. While premature death is usual in CF, even in the presence of severe lung disease, prognostication is not accurate. While an FEV_1 of <30% has been associated with death within 2 years, this does not apply to all patients.

Even in the late stages of the disease when it has become clear that the person is in an advanced state of decline, management may have preventive (e.g. vitamin supplementation), therapeutic (e.g. antibiotic therapy) and palliative (e.g. opioid use) components. Decision-making at this time may be complicated by questions surrounding lung transplantation. Even where transplantation may be considered, this should not be a barrier to providing proper end of life care. However, a cure-focused possibility can be entertained at the same time as a more palliative approach so that there are no regrets on either side (family and medical team) if the transplant does not happen. It is important not to instil false hope if this is clearly not likely to happen.

Defining when palliative care should dominate is difficult but needs to be done if the sufferer and family are to have the best chance of coping with death, dying and the grieving process. Thus sensitive and honest discussion around therapeutic options and the purpose of all interventions needs to take place. It is helpful to define the goals of care, and explore the motives of patient, family and team for each aspect of care. Unnecessary suffering through instituting or prolonging purposeless ('futile') interventions must be avoided. It is important that the caring team and the patient and family understand and agree on any treatment plan.

Advance care planning for emergency situations is recommended to avoid inappropriate levels of care being given. Such interventional measures are often very traumatic to patient and family.

11.7.1 Prevention and treatment of symptoms

The help of hospice organisations, counsellors or a palliative care team should be sought early in the end of life stage of the disease. Defined and open channels of communication between the family and caring teams should be established at this stage.

11.7.1.1 Physical discomfort

Dyspnoea is the dominant physical symptom. Management options include domiciliary oxygen, opioids (oral, subcutaneous or intravenous) and anxiolytics (oral of buccal). While opioids may suppress respiration, fear of this should not prevent adequate dosing which is usually below that required for pain. In certain circumstances non-invasive ventilation may be considered (see Section 5.5.7, p).

Difficulty clearing secretions may be overcome with positioning, saline inhalations and gentle physiotherapy. There is some evidence that oral steroid therapy may help. Suction is usually not tolerated.

Pain (especially headache) is common and should be treated with titrated doses of non-steroidal analgesics and/or gabapentin. Addiction is not a risk but many families fear this, resulting in unnecessary suffering for the dying individual. Complementary therapies may play a major role in promoting comfort. Anxiety aggravates pain and dyspnoea.

Clonidine which has anxiolytic as well as analgesic properties is useful in CF palliative care.

Sleep disturbance is common. Mild sedatives should be encouraged. Melatonin can help. Fears (e.g. dying unsupported in the middle of the night, concerns about those who will survive the individual) should be allayed where possible.

Management of **fever** is important as this can add to discomfort. Add ibuprofen to paracetemol if necessary. Suppositories are useful if a child unable to swallow.

11.7.1.2 Emotional discomfort

Anxiety, fear and depression are all common in the late stages of CF. Good communication between family members and with the therapeutic team is essential. Decisions around where the sufferer will die need to be taken. Anxiolytics and antidepressants can be helpful. In consultation with the patient, unnecessary and burdensome therapies should be withdrawn. This requires regular discussion.

11.7.1.3 Spiritual discomfort

Open and honest discussion of spiritual concerns should be encouraged. Involvement of counsellors from religious groups acceptable to the patient and family is helpful.

The relationship between parents and the health team need not end at the time of the CF patient's death. Families should feel free to contact the CF team at any time; teams should encourage such follow up interactions.

12. THE HEALTHCARE TEAM

Many people are involved in the management of the CF patient. The patient, parents and relatives must carry out the actual treatment that has been prescribed by the CF team at the hospital. Their understanding of the treatment prescribed and the reasons for the treatment is absolutely essential if the patient and those at home are to be motivated to comply with the treatment advised. The better the patient and relatives understand a particular treatment, the more efficiently it will be carried out.

12.1 CF CENTRES

All CF patients should be known to and have access to specialist advice from a CF clinic. Specialist CF clinics should be set up in each region at tertiary hospitals (ideally one clinic for children and one for adults). The clinic must have a multidisciplinary team including CF specialist doctors and nurses, a physiotherapist, a dietician, genetic counsellor and a mental health professional (social worker or psychologist). Access to surgical, radiological, pharmaceutical and laboratory expertise is essential.

All patients living within reasonable distance of a specialised CF clinic should attend these for most of their CF care and advice.

12.2 SHARED CARE

A satisfactory pattern of care for patients who live some distance from the regional CF Units is "shared care". A comprehensive assessment at the CF clinic each year or so, with the rest of the care being given at the local hospital, works well for some patients with co-operative and knowledgeable local doctors.

12.3 ALTERNATIVE THERAPY

There is no major objection to using any alternative therapy provided it does NOT counteract/contradict or distract from regular, conventional accepted therapies. Dietary therapy, vitamin or trace element supplementation, or homoeopathy may all be useful, provided they are used in combination with conventional therapies. Spiritual healing techniques are often used and may prove to be helpful, if only to improve attitude of the patient and to provide a positive attitude and hope for the future. Self hypnosis and massage therapy have been used for relaxation and pain and headache relief. Herbal remedies (e.g. Ginseng) may cause the activation of neutrophils enhancing the clearance of and modulating the immunoglobulin response to *P aeruginosa*.

Remember - NO ALTERNATIVE THERAPY CAN REPLACE CONVENTIONAL THERAPY.

APPENDICES

Antibiotic doses are usually given in higher doses and for longer durations in CF children. This is because of differences in pharmacokinetics and pharmacodynamics. There is also the presence of underlying lung disease to consider.

APPENDIX 1: ORAL ANTIBIOTICS

DRUG	DOSE	FREQUENCY	COMMENTS
Amoxycillin	100mg/kg/day Adult 500mg tds	3 divided doses	Rashes and loose stools may occur. 20% *H influenzae* are resistant to Amoxil in parts of SA Maximum dose: 6g/day
Azithromycin	Short term treatment only: Child 10mg/kg po for 3 days Adult: 500mg po for 3 days **For chronic suppressive treatment** **<** 15 kg : 10mg/kg 15-40 kg: 250mg (not/kg) >40kg : 500mg (not/kg)	 Daily Daily Once a day for 3 days per week Once a day for 3 days per week	Give on an empty stomach Potential for hepato- and ototoxicity but usually very well tolerated. No additional anti-staphylococcal prophylaxis needed when maintained on this long term.
Cefuroxime	10mg/kg/dose (*not/kg*)	2 divided doses	
Ciprofloxacin	>5 years: 40mg/kg/day orally <5 years: 30mg/kg/day Adult: 1.5-2g/day	2 divided doses	Drug interactions with theophylline and other drugs. Photosensitivity is common. C/I patients with joint disease. Max: 3g/day. Sun protection should be taken for 4 weeks after completion of course.
Clarithromycin	<8kg: 15 mg/kg/day 1-2yrs: 62.5mg/dose (*not/kg*) 3-6yrs: 125mg/dose *(not/kg)* 7-9yrs: 187.5mg/dose *(not/kg)* >10yrs: 250mg/dose (*not/kg*)	2 divided doses	Suitable for use when erythromycin is not tolerated. Can cause tooth and tongue discolouration. Active against *S aureus* and *H influenzae.* Used in the treatment of non-TB mycobacteria (NTM)
Clindamycin	20-30 mg/kg/day	3-4 divided doses	Max 2.4g/day. GIT effects. Rarely pseudomembranous colitis. Advise stop if diarrhoea.

Co-amoxy-clavulanate	<6 yrs: 0.5 ml/kg/dose of 125/31 suspension 6-12 yrs: 10 ml/dose of 250/62 suspension 12-18 yrs: 1 tablet/dose of 500/125 tabs.	3 doses/day	Give for at least 2 weeks. Care with CF liver disease Active against *S aureus* and *H influenzae.*
Co-trimoxazole	<6 months: 240 mg/dose 6 months – 6 years: 480 mg/dose 6 -12 yrs: 960 mg/dose >12 yrs: 1920 mg/dose	2 doses/day	Can be used for treatment and eradication of MRSA. Also used in the treatment of *S maltophilia.* Can cause allergic reactions. Report any rashes or fever.
Erythromycin	<2 yrs: 500 mg/day (*not/kg*) 2-8 yrs: 1g/day (*not/kg*) >8 yrs: 1-2g/day (*not/kg*)	4 divided doses	
Flucloxacillin	50-100 mg/kg/day	3-4 divided doses	Max 4g/day
Sodium fusidate	50mg/kg/day as fusidate	3 divided doses	***Note:*** *Susp. Is in form of fusidic acid 250mg/5mls (therapeutically equivalent to 175mg sodium fusidate).* Caution in liver disease. Use with another antibiotic to avoid resistance. Max: 2.25g.day
Linezolid	< 12 years 10mg/kg/dose (max 600mg) >12 years 600mg	3 doses/day 2 doses/day	Used in the treatment of *MRSA* or *S aureus* where patient has not responded to other agents. Courses >28 days have risk of optic neuropathy. Baseline and follow-up ophthalmic examinations recommended. Patient should report any visual changes.
Rifampicin	10 mg/kg (max 600mg)	2 doses/day	Used in treatment and eradication of MRSA. Second line for *S aureus.* Usually used in combination with fusidic acid. Caution in CF liver disease. Causes red staining of urine, tears and saliva.

APPENDIX 2: INTRAVENOUS ANTIBIOTICS

Note: The Pharmacokinetics and Pharmacodynamics of the individual drug need to taken into account when using these drugs in cystic fibrosis. Refer to Section 5.1.2 for guidelines on when to use these drugs. Consult an expert when additional problems such as renal impairment exist as dosages will vary.

DRUG	DOSE	FREQUENCY	COMMENTS
Amikacin	35mg/kg/day	Daily	Peak 25-30mg/l taken 1 hr post-dose. Trough <2 g/ml for daily dosing. Max starting dose 1g daily
Aztreonam	200-250mg/kg/day	3-4 divided doses	Max 8g/day
Cefepime	150-200mg/kg/day Adult: 2g stat then 6g.day	3 divided doses run as continuous infusion.	Maximum of 4g/day
Ceftazidime	150-300mg/kg/day Adult: 2g stat then 6g/day	3 doses per day run as continuous infusion.	Max 9g/day
Ciprofloxacin	<5 years: 8-16mg/kg/day 5-17 years: 30mg/kg/day Adult 800mg	2 divided doses. 2 divided doses	< 5years: Max 800mg/day Adult: Maximum 1.6g/day
Colistin	75000 units/kg/day Adults >40kg: 9MU bolus, then 9MU/day	2 divided doses 2 or 3 divided doses (2 doses may have fewer adverse effects)	Bolus dosing of 9 MU in 10ml 0.9% NaCl over 5 mins recommended for patients >40kg. **Always use colistin with another antibiotic group e.g.-lactam**
Clindamycin	30-40mg/kg/day	3 divided doses.	Max 2.7g/day
Gentamicin	10-12mg/kg/day	Daily	Maximum 480mg/day until levels known. Peak 10-12mg/l Trough <2mg/l
Imipenem	90mg/kg/day 1,5 - 3g/day	3 divided doses infused over 2-3 hours	Max 4g/day. Use the higher dose for sicker patients
Linezolid	<12 yrs:10 mg/kg (max 600mg) >12 yrs: 1.2g/day (max 600mg)	<12 yrs:3 divided doses >12 years: 2 divided doses	Infuse over 30-120mins. Courses >28days – risk of optic neuropathy. Only to be used for MRSA or *S aureus* where patients have not responded to conventional agents. Use oral route where

Meropenem	120mg/kg/day Adult: 2g stat then 6g/day	3 divided doses infused over 3 hours	Maximum 6g/day. Bolus or infusion. Associated with headaches.
Piperacillin-Tazobactam	Child: 300mg/kg/day Adult: 4.5g stat then 18g/day/day	2 or 4 doses per day run as continuous infusion	Hypersensitivity/skin rashes
Teicoplanin	10mg/kg/dose Adults 400mg/dose	12hrly for first 3 doses then once daily 12hrly for first 3 doses then once daily	Dose can be increased to 15mg/kg in severe infections. Measure drug levels.
Tobramycin	10 mg/kg	Daily	Max 600mg. Infusion over 20-30 mins. Serum trough level <1.5mg/l. If level raised, omit next dose and re-measure. If previous course had raised trough level reduce dose by 20%.
Vancomycin	45mg/kg/day	4 divided doses	MUST be infused over minimum of one hour (monitor levels). Trough 5-10mg/l; Peak 18-25mg/l

APPENDIX 3: ANTIFUNGALS

Amphotericin (nebulised)	10mg 2-4 times a day or 25mg bd	Dissolve injection with water, not saline. Dilution 50mg in 10ml water. 1ml=5mg.
Amphotericin (intravenous)	Start 1mg/kg od then increase to 5mg/kg od over 3 days.	Give test dose 100mcg/kg (max1mg) over 10mins and observe for 30mins. Check renal and liver function at least 3/week. Use with caution with other nephrotoxic antibiotics. Used for invasive *Aspergillus*.
Caspofungin (intravenous)	<3 months: 25 mg/m2 3months - 1yr 50 mg/m2 >1 yr 70 mg/m2 (max 70mg) day 1 then 50 mg/m2 (max 70mg). This can be increased to 70 mg/m2 (max 70mg) if lower dose is tolerated but inad-equate response	3rd line agent for invasive aspergillosis. Used if intolerance or poor response to amphotericin. Very expensive. Infuse over 60mins. Incompatible with glucose solutions.

Itraconazole	1 month to 12 years: 2.5 mg/kg bd (Can also use 5 mg/kg daily) >12 years: 200mg bd	Take with cola or other acidic liquid. Stop antacids if possible, or give 1 hour later. Consider monitoring LFTs. Consider monitoring levels (ideal trough serum level is 0.5-1mg/l).
Voriconazole	<12 yrs: 6 mg/kg bd (max 200 mg)for 1 day, then 4 mg/kg bd (max 100mg) >12 yrs (<40 kg): 200 mg bd for 1day, then 100 mg bd >12 yrs: (>40 kg) 400 mg bd for 1day, then 200 mg bd	Warn of photosensitivity and temporary visual problems Monitor LFTs.

APPENDIX 4: NEBULISED ANTIBIOTICS		
Amikacin	<10yrs: 250mg bd >10yrs: 500mg bd	Use injection and make up volume to 4ml with saline.
Aztreonam Lysine	75mg tds for 28days	Not licensed under 18years. Currently not available.
Ceftazidime	1gm bd	Reconstitute 1gm with 3ml water. Used for *B cepacia*
Colomycin (Colistin)	<2years: 500000 units <10 yrs: 1 megaunit >10 yrs: 2 megaunits bd	For a dose of 1 megaunit make up to 4ml with saline. Dose can be increased to 2 megaunits in 4ml saline. Pre-dose with bronchodilator.
Gentamycin	<5yrs: 40mg bd >5yrs: 80-160mg bd	Use injection and make up volume to 4ml with saline.
Tobramycin	5-10 yrs: 80mg bd >10yrs: 160mg bd	Use injection and make up volume to 4ml with saline.
TOBI^{R}	300mg bd alternate months	Licensed >6years only
Vancomycin	250mg/4ml over 10mins bd	Used in the treatment and eradication of *MRSA* and *S Aureus*

APPENDIX 5: OTHER NEBULISED DRUGS		
BRONCHODILATORS		
Salbutamol 2.5mg/2.5ml 5mg/2.5ml	6mths-5yrs: 2.5mg >5yrs: 5mg	Repeat up to 6 times daily.
STEROIDS		
Budesonide 250 g/ml 500 g/ml	3mths-12yrs: 0.25-1mg bd 12yrs: 1mg bd	
MUCOLYTICS		
Hypertonic saline	2-4 mls of 5% or 7% solution	Up to twice per day 30 mins before physiotherapy
rhDNase	2.5mg (1 vial) daily	Dose can be increased to twice per day if necessary.

APPENDIX 6: GASTROINTESTINAL TRACT

MECONIUM ILEUS EQUIVALENT (DIOS)

N-acetylcysteine	5-10ml qds in orange juice. Adults: 30ml tds with 120ml water or orange juice.	Can also be given rectally.
Oral Gastrografin®	Day 1: <15kg 25ml 15-25kg: 50ml >25kg: 100ml in 4 times the volume of water or fruit squash i.e. 200-400ml Day 2 and 3; half Day 1 dose	Can also be used rectally under x-ray supervision. Dilute enema 3-5 times with water. Hydration of patient is essential. Do not use in presence of bile stained vomiting.
Rectal Gastrografin	Same dose as oral. <5years:diluted to 5times volume with water. >5years:diluted to 4 times volume with water. 1 sachet to 1liter water- can flavour with clear cordial	Need to give IV fluids when administering. Given orally or via NG tube. Rate up to 25ml/kg/hour.
Klean-prep Golytely		Maximum volume 100ml/kg or 4litres over 4 hours until clear fluid passed per rectum. Monitor for hypoglycaemia.

CONSTIPATION

Lactulose	1-5 years: 5 ml bd 5-10 years: 10 ml bd >10 years: 15-20 ml bd	Adjust dose according to response.
Movicol	1 - 6 years: 1 sachet of Movicol **Paediatric Plain** OD.Maximum 4 sachets daily. 7 - 12 years: 2 sachets of Movicol **Paediatric Plain** OD. Maximum 4 sachets daily. 13 - 18 years: Initially 1 - 3 sachets of Movicol per day in divided doses for up to 2 weeks. Maintenance dose 1-2 sachets daily.	Used in chronic constipation to prevent faecal impaction. Mix Paediatric Plain with 60-65ml water. Mix Movicol with 125ml water

ACID SUPPRESSION

Omeprazole	0.7-1.4mg/kg/day Adult maximum 10mg tds	Swallow whole or open capsule and mix contents with fruit juice or yoghurt.
Ranitidine	4mg/kg/day in 2 divided doses.	Maximum: 300mg bd.

LIVER DISEASE

Ursodeoxycholic acid	20mg/kg/day in 2-3 divided doses	Take with or after food. Rare side-effect is diarrhoea.

APPENDIX 7: PANCREATIC ENZYMES

Number of Units per Capsule

	LIPASE	PROTEASE	AMYLASE
CREON®	10,000	600	8000
CREON 25000®	25,000	1000	18000
PANKREASE®	5000	330	2900

APPENDIX 8: FAT SOLUBLE VITAMINS

Daily recommended dose

Age	Vitamin A 1µg =3.3IU	Vitamin D 1µg =40IU	Vitamin E (200u = 134mg)
< 1year	4000IU (1200µg)	400IU (10µg)	10 – 50mg
>1year	4000 – 10000IU (1200-3000µg)	400-800IU (10-20µg)	50 – 100mg
Adults	4000-10000IU (1200-3000µg)	800-2000IU (20-50µg)	100 – 200mg

APPENDIX 9. NUTRITIONAL SUPPLEMENTS

ADULT FEEDS				
	Nutricia	Abbott	Fresenius	Nestle
Polymeric feeds (1kcal/ml) Powdered		Ensure		Nutren Activ, Nutren Optium
Polymeric feeds (1kcal/ml) Ready to use	Nutrison standard	Osmolite	Fresubin original	
Feeds with fibre	Nutrison multi fibre		Fresubin with fibre	Nutren with fibre
Polymeric (1.2 to 1.5 kcal/ml)	Nutrison energy	Ensure plus	Fresubin HP energy	
Feeds with fibre	Nutrison protein multi fibre	Jevity plus	Fresubin energy fibre	
Modular feeds				
Carbohydrate	Frantomalt	Polycose		
Protein	Protifar			
Fat	Calogen, Duocal, MCT oil		MCT oil	

PAEDIATRIC FEEDS				
Powdered		Pedisure		Nutren junior
Ready to use	Nutrini	Pedisure plus	Tentrini	
Specialised products				
Powdered		Alitraq (semi elemental with glutamine), Glucerna SR (diabetic)		Peptamin (semi elemental) for adults and children Nutren diabetes
Ready to use	Nutrison advanced peptisorb (semi elemental) Nutrison advanced diason (diabetic) Infatrini (energy dense feed)	Oxepa (EFA and antioxidants), Glucerna (diabetic)	Surivmed (semi elemental) Fresubin diaben (diabetic)	Peptamen (semi elemen-tal) adult and junior. HP and advanced

APPENDIX 10: DESENSITISATION REGIMEN

Piperacillin/Tazobactam (Tazocin®) (per continuous infusion)

1st give 100mg over 6 hours
2nd give 500mg over 6 hours
3rd give 2g over 6 hours
4th give normal adult dose (13.5g / 24hours)

Ceftazidime (per continuous infusion)

1st give 50mg over 6-8 hours
2nd give 250mg over 6-8 hours
3rd give 1g over 6-8 hours
4th give normal adult dose (100 mg/kg/24hour or 6g/24 hours)

From the beginning to the end of treatment patients should be on H1 & H2 receptor blockers i.e. Cetirizine 20mg twice per day po, Ranitidine 600mg twice per day po.

APPENDIX 11: CONTACT INFORMATION

CYSTIC FIBROSIS CLINICS

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Dr Dave Richard (Paediatric Pulmonologist)
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Groote Schuur Hospital
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Prof Paul Willcox (Pulmonologist)

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Universitas Academic Hospital
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Greenacres Hospital
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CHARITY ORGANISATIONS THAT SUPPORT CYSTIC FIBROSIS CLINICS, PATIENTS & THEIR FAMILIES

SOUTH AFRICAN CYSTIC FIBROSIS ASSOCIATION

www.sacfa.org.za

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Cape Town	Ruth Ireland: 021 557 0323; sacfact@mweb.co.za
KZN	Ashleigh Robertson: 071 602 2966; ashleighr@mweb.co.za

SOUTH AFRICAN CYSTIC FIBROSIS TRUST

www.sacftr.co.za
011 0222 464

SOUTH AFRICAN CYSTIC FIBROSIS REGISTRY

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