THE SOUTH AFRICAN CYSTIC FIBROSIS CONSENSUS GUIDELINES

FIFTH EDITION, 2017

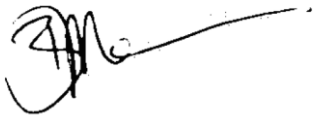
FOREWARD

It is a great privilege to present the 5th edition of the South African Cystic Fibrosis (CF) Consensus guidelines on behalf of the CF Medical and Scientific Advisory Committee, the SA CF Association and the panel of experts who have graciously contributed their valuable time and expertise to these comprehensive guidelines. The importance of producing and disseminating up to date CF guidelines relevant for South Africa cannot be overstated. The great strides in improving the overall outlook for people with CF across the world is partly attributed to translating evidence-based science into practise through the generation of guidelines that encourage healthcare providers to practice evidence-based medicine. Furthermore, these guidelines will continue to serve as an important tool to advocate for access to healthcare services and interventions in the SA setting where CF is regarded an orphan disease competing for scarce resources with a growing burden of non-communicable diseases overwhelming the health system. South Africa has unique circumstances and socio-economic challenges that impact on the health and care of people with CF. Simply adopting existing international guidelines for our setting may therefore not always be relevant or appropriate.

This edition coincides with an exciting time in the world of CF where significant advances have been made in recent years towards finding a cure, through the development and registration of new drugs that target the specific genetic defect causing CF. In addition to updating previous chapters, this edition introduces new concepts and guidelines for diagnosing CF, discusses some of the novel drugs introduced in international circles and expands on topics that are increasingly important and relevant to adults living with CF, who now outnumber children due to improving outcomes.

We thank all the contributors to this edition, colleagues and members of the CF community who continue to support our efforts to ensure people with CF in SA receive world-class and up to date care. In addition, we thank Abbot for their generous support in the production and dissemination of these guidelines.

Sincerely



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AIM OF THE CF CONSENSUS DOCUMENT (2017)

Cystic Fibrosis (CF) is a complex multisystem disorder that requires continuous multi-disciplinary management and disease monitoring by professionals with experience and expertise in the field. The outcome and life-expectancy of individuals living with CF internationally has greatly improved through dedicated implementation of evidence-based interventions and novel treatments. In South Africa, CF is considered an orphan disease and thus struggles to receive recognition and resources required to advocate and advance CF. Furthermore, financial and staffing constraints present challenges to managing CF in South Africa. The aim of this document is to present up to date consensus expert opinion and evidence-based guidelines 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 in both the private and public sectors. References are available on request from the editors.

TARGET AUDIENCE

- People with CF and their families
- General practitioners and specialists diagnosing and treating people with CF
- Physiotherapists
- Dieticians
- Mental health professionals and social workers
- Health service administrators and funders
- Nurses
- 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.

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The valuable contributions of SACFA are gratefully acknowledged:

- Mr Alan Dunn (President)
- Mr George Pearson (late past Executive Officer)
- Mr Alain Woolf (past President)

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CHAPTER 1: INTRODUCTION

Cystic fibrosis is one of the more common life-limiting genetic diseases in South Africa and occurs 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 well into adulthood. With recent advances in CF care, there is renewed hope for people with CF and their families, with the discovery of gene-directed therapies which target basic genetic problem.

1.1 THE BASIC PROBLEM

The basic abnormality in CF is an inheritance of two abnormal CF genes (one from each parent) which result in abnormalities in the cystic fibrosis transmembrane regulator (CFTR) protein. The CFTR protein is a critical protein, whose function is the regulation of movement of chloride across the epithelial membranes in the body. CFTR is a very complex protein made up of five major components; the two nuclear binding domains (NBD), two membrane bound regions and a regulatory (R)-domain which is between the NBDs.

There is also evidence that in people with CF, the epithelial sodium channel (ENaC), which controls the movement of sodium across epithelial membranes is also affected. Movement of water across cell membranes is dependent on the correct function of the chloride and sodium channels. The defects in CF described above result in poor movement of water across the epithelial cell surfaces; which causes the secretions produced by many organs of the body to be dehydrated and sticky.

The major target organs that are affected by CF are the lungs, pancreas, liver, reproductive system, sweat ducts and the bowel. In CF, the sweat glands produce an increased amount of sodium and chloride which forms the basis of diagnosing CF through a sweat test.

The lungs are the most important organs affected in CF and largely responsible for the limited life-span associated with CF. Dehydrated sticky airway secretions and impaired mucociliary clearance predisposes to colonisation of the airways by micro-organisms and persistent inflammation. Chronic infection and inflammation leads to progressive structural airway and lung parenchymal damage, and ultimately respiratory failure.

Obstruction of the pancreatic ducts by sticky secretions leads to similar inflammation and destruction of pancreatic tissue, usually before birth. Pancreatic enzymes are required for the digestion of fats and proteins for most people with CF. Exocrine pancreatic insufficiency results in fat/protein malabsorption and malnutrition. Fortunately, with modern pancreatic enzyme treatment, the majority of infants and children can attain normal growth and nutrition. The endocrine function of the pancreas is usually preserved in early life but progressive pancreatic destruction in later life may result in CF-related diabetes mellitus.

CF is a multi-organ disorder, requiring continuous use of multiple therapies to prevent and minimise organ damage. A fundamental principle for optimal CF care is a multidisciplinary team (MDT) approach within the framework of specialised CF centres. Use of a MDT approach has resulted in prolonged and improved quality of life of people with CF. Other healthcare professionals such as general practitioners and specialists should be encouraged to participate in a 'shared care' arrangement with these teams.

CHAPTER 2. CLINICAL PRESENTATION

The phenotypic presentation of CF is variable, even in patients with the same genotype and it is influenced by several factors including age, genotype and socioeconomic circumstances. “Typical” CF presents in 85% of individuals as pancreatic insufficient (PI) CF with the classical features malabsorption, growth faltering and pulmonary disease. Pancreatic sufficient (PS) CF presents with predominantly respiratory disease (see table 2.1).

Molecular advances in understanding the wide range of functional classes in CFTR dysfunction has led to a greater awareness of milder and atypical presentations of CF than were previously recognised.

COMMON PRESENTATIONS OF CYSTIC FIBROSIS

MECONIUM ILEUS

CF can present with a delay in passage of meconium after birth. Meconium is passed by neonates immediately after delivery and in about 80% of all babies this is passed in the first 24 hours of life. In 15% to 20% of newborn infants with CF, the bowel is blocked by sticky meconium. There may be signs of intestinal obstruction antenatally on ultrasound, and/or 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 advances in neonatal surgery, anaesthesia and nutritional support.

INTESTINAL MALABSORPTION / POOR WEIGHT GAIN

About 85% of individuals with CF have malabsorption due to pancreatic insufficiency, and in most cases, this presents in infancy. These infants present with steatorrhoea (offensive, fatty stools) or loose stools, poor growth and failure to thrive despite adequate nutritional. Occasionally, oedema is present and the clinical picture resembles that of kwashiorkor. Hyponatraemia and hypochloraemic metabolic alkalosis is a common presentation in infants with CF.

CHEST INFECTIONS

Most people with CF have recurrent chest infections or wheezing, usually from an early age. The viscous mucus obstructing the airways leads to excessive (often productive) cough and recurrent and chronic bacterial lung infections, which, once established may be difficult to eradicate. The consequence of chronic airway infection is bronchiectasis and structural lung damage.

Table 2.1 shows the range of presenting features of CF by age. The most common 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.

TABLE 2.1. COMMON PRESENTATIONS OF CF BY AGE

ANTENATAL (WITH ULTRASOUND SCANNING):

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

NEWBORN:

- Meconium ileus
- Meconium plug
- Ileal and other intestinal bowel atresias
- Meconium peritonitis

INFANT AND CHILD:

- Recurrent chest infections or wheeze
- Persistent chest symptoms/pneumonia with slow response to antibiotics
- Severe “bronchiolitis”
- *Pseudomona*s 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 metabolic alkalosis
- Hyponatraemic dehydration/heat prostration
- Pseudo-Bartter syndrome

ADOLESCENT AND ADULT:

- Chronic obstructive airways disease
- Persistent chest symptoms/pneumonia with slow response to antibiotics
- Uncontrolled “asthma”
- Bronchiectasis
- *Pseudomonas aeruginosa* isolated from the respiratory tract
- Sinusitis
- Nasal polyposis
- Male infertility/azoospermia
- Recurrent pancreatitis

COMMON PRESENTATIONS IN ATYPICAL CYSTIC FIBROSIS OR CFTR DYSFUNCTION (SINGLE ORGAN DISEASE PHENOTYPE):

- Male infertility (due to congenital bilateral absence of the vas deferens - CBAVD)
- Chronic or recurrent pancreatitis
- Allergic bronchopulmonary aspergillosis (ABPA)
- Mild isolated bronchiectasis
- Diffuse panbronchiolitis
- Neonatal hypertrypsinoginaemia
- Sclerosing cholangitis

In these cases, sweat tests may be negative or in the intermediate zone but two disease-causing CFTR mutations are present. Close follow up and genetic counselling is advised to screen for evolving manifestations of atypical CF disease or CFTR dysfunction.

CHAPTER 3. CF GENETICS AND GENETIC TESTING

CF is a genetic disease, inherited in an autosomal recessive manner. This means 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 CF gene can be passed down in families for many generations without being detected.

In South Africa, approximately 1 in 27 individuals in the Caucasian population, 1 in 55 in the population of mixed ancestry and up to 1 in 90 black Africans carry a CF mutation. It is estimated that 1 in 2 000 Caucasian babies, 1 in 12 000 babies of mixed ancestry and up to 1 in 32 000 black African are born with CF in South Africa. For a couple who are both carriers of a CF gene, each pregnancy has a 1 in 4 chance of producing a foetus/baby with CF. The parents are called *obligate carriers* of a faulty gene for CF (Figure 3.1). The risk of conceiving a child with CF is significantly increased if a parent has CF.

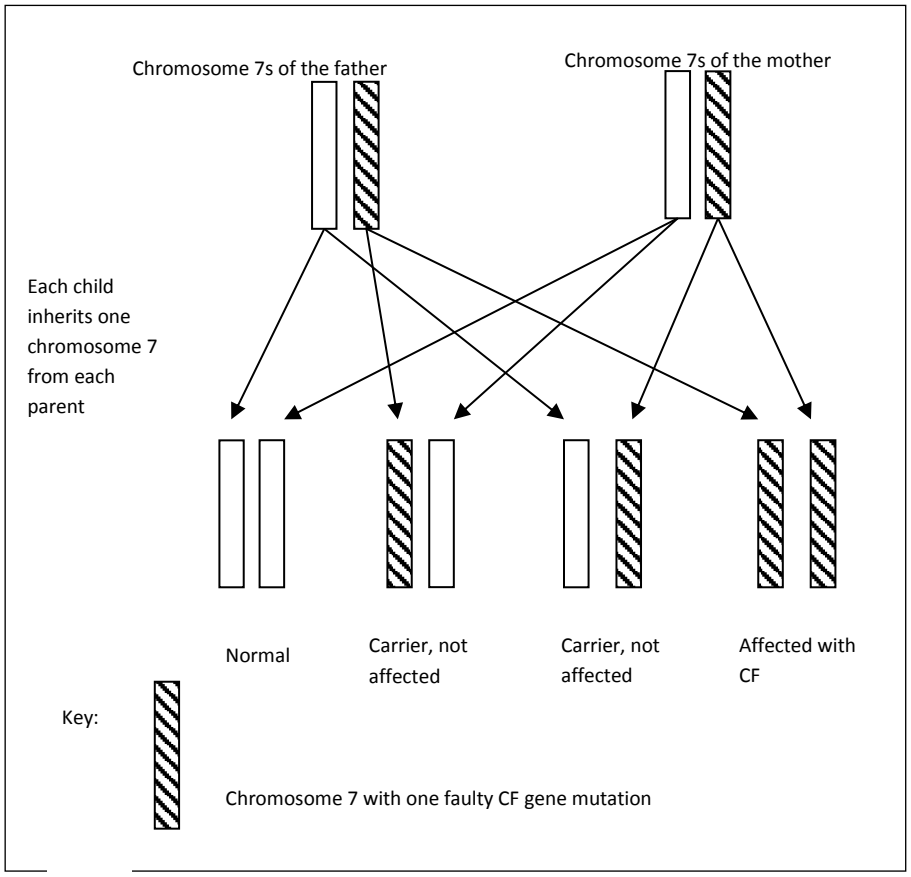

FIGURE 3.1: AUTOSOMAL RECESSIVE INHERITANCE OF THE FAULTY GENE FOR CF, SHOWING A 1-IN-4 CHANCE WITH EACH PREGNANCY OF HAVING A CHILD AFFECTED WITH CF

3.1 GENETIC TESTING FOR CFTR MUTATIONS

The CF gene has been identified on the long arm of chromosome number 7. A mutation is a mistake or change in the DNA sequence of a gene that causes it to malfunction. More than 2 000 CFTR mutations and variants have thus far been described, but not all are necessarily disease-causing mutations. The Cystic Fibrosis Foundation's updated Consensus Statement on CF diagnosis has recommended the following broad classification of CFTR mutations and has adopted **CFTR2 database** (https://www.cftr2.org/index.php) as its reference. Healthcare providers are encouraged to refer to CFTR2 to determine the significance of any new or uncommon CFTR mutation or variant that is identified. Consultation with a CF expert and genetic counsellor is recommended when a CFTR variant of unknown significance is identified:

- CF- causing mutation: results in CF when two copies are present in an individual
- Mutation of varying clinical consequence (MVCC): a mutation that in combination with a CF-causing mutation or another MVCC may result in CF
- Mutation of unknown clinical consequence; not evaluated by CFTR2
- Non-CF causing mutation

The most common mutation in the Caucasian and mixed-race population in South Africa is p.Phe508del (previously known as ΔF508), present in 70-80% and 65% of carriers in these respective population groups. The most common mutation described thus far in the black African population is c.2988+1G>A (previously known as 3120+1G→A).

It is important to know which mutation(s) is/are present in a family with CF, especially when a sibling or other family member is planning their own family. If an individual is a known CF carrier, their partner should be tested to assess the couple's risk of having a child with CF. Carrier testing can be performed on anybody, with or without a family history of CF, through testing a blood sample after appropriate genetic counselling.

Individuals who may also be at increased risk of having children affected with CF include more distantly related family members and couples from consanguineous marriages (marriages between related individuals.

LABORATORY METHODS TO TEST FOR CFTR MUTATIONS

Laboratories in the public and private sectors may use different methodologies. Genetic testing for CF can be done by two methods: 1) testing for the most common mutations within a specific population groups using a commercial laboratory kit of 30 or 50 known mutations, or 2) full sequencing of the CFTR gene. Commercial kits were developed for European populations, and this must be borne in mind when requesting genetic testing in the SA setting with its genetic diversity.

Sequencing of the whole CFTR gene is now offered in more SA laboratories. This approach may be more appropriate when two CFTR mutations have not been identified using commercial kits and there is clinical suspicion of CF in order to detect uncommon or previously unidentified mutations (or sequence variants).

New genetic terminology with next generation sequencing has been introduced. Table 3.1 summarises the mutations included in the various commercial CF kits with old and new nomenclature.

TABLE 3.1: LIST OF CFTR MUTATIONS WITH LEGACY AND STANDARD NOMENCLATURE, AND KITS CURRENTLY USED FOR TESTING IN SA

Legacy (old) nomenclature	cDNA / protein nomenclature	CF30 kit	CFTR Core	CF Genotyping Assay
Y1092X	3276C>A / p.Tyr1092X	√	√	
1717-1G>A	c.1585-1G>A	√	√	√
G542X[1]	c.1624G>T / p.Gly542X	√	√	√
W1282X[1]	c.3846G>A / p.Trp1282Arg	√	√	√
N1303K[1]	c.3909C>G / p.Asn1303Lys	√	√	√
ΔF508[1,3]	c.1521_1523delCTT / p.Phe508del	√	√	√
3849+10kbC>T[1]	c.3717+12191C>T	√	√	√
394delTT[1]	c.262_263delTT / p.Leu881IlefsX22	√		√
621+1G>T	c.489+1G>T	√	√	√
S1251N	c.3752G>A / p.Ser1251Asn	√		
G551D	c.1652G>A / p.Gly551Asp	√	√	√
R117H	c.350G>A / p.Arg117His		√	√
R1162X	c.3484C>T / p.Arg1162X	√	√	√
R334W	c.1000C>T / p.Arg334Trp	√	√	√
A455E	c.1364C>A / p.Ala455Glu	√		√
2183AA>G	c.2051_2052delAAinsG / p.Lys684SerfsX38	√	√	√
3659delC	c.3528delC / p.Lys1177SerfsX15	√	√	√
1078delT	c.948delT / p.Phe316LeufsX12	√	√	√
I507del	c.1519_1521delATC / p.Ile507del	√	√	√
R347P	c.1040G>C / p.Arg347Pro	√	√	√
R553X	c.1657C>T / p.Arg553X	√	√	√
E60X	c.178G>T / p.Glu60X	√		
1811+1.6kbA>G	1679+1.6kbA>G	√		
3272-26A>G[1]	c.3140-26A>G	√	√	
2789+5G>A	c.2657+5G>A	√	√	√
3120+1G>A[2,3]	c.2988+1G>A	√	√	√
711+1G>T	c.579+1G>T	√	√	√
G85E	c.254G>A / p.Gly85Glu	√	√	√
Y122X	c.366T>A / p.Tyr122X	√		
W846X	c.2537G>A / p.Trp846X	√		
CFTRdele[2,3]**(21kb)**	c.54-5940_273+10250del21kb / p.Ser18ArgfsX16		√	
1898+1G>A	c.1766+1G>A		√	√
R560T	c.1679G>C / p.Arg560Thr		√	√
L1077P	c.3230T>C / p.Leu1077Pro		√	
R117C	c.349C>T / p.Arg117Cys		√	
L1065P	c.3194T>C / p.Leu1065Pro		√	
R347H	c.1040G>A / p.Arg347His		√	√
T338I	c.1013C>T / p.Thr338Ile		√	

I336K	c.1007T>A / p.Ile336Lys		√	
1677delTA	c.1545_1546delTA / p.Tyr515X		√	
2184insA	c.2052_2053insA / p.Gln685ThrfsX4		√	
2143delT	c.2012delT / p.Leu671X		√	
IVS8: 5/7/9T	VARIANT*		√	√
2184delA	c.2052delA / p.Lys684AsnfsX38			√
S549N	c.1646G>A / p.Ser549Asn			√
S549R	c.1647T>G / p.Ser549Arg			√
V520F	c.1558G>T / p.Val520Phe			√
3876delA	c.3744delA / p.Lys1250ArgfsX9			√
3905insT	c.3773_3774insT / p.Leu1258PhefsX7			√
F508C	c.1523T>G / p.Phe508Cys			√
I506V	VARIANT*: c.1516A>G / p.Ile506Val			√
I507V	VARIANT*:c.1519A>G / p.Ile507Val			√
I508C	VARIANT*: c.1523T>G / p.Phe508Cys			√

*[1]common in SA Caucasian population; [2] found in SA Black African population; [3]common in Caucasian and SA Mixed Race populations; *Variant is a change in the DNA sequence which has an unknown pathogenicity and may contribute towards the phenotype*

3.2 PRENATAL DIAGNOSIS

Reliable prenatal diagnosis of CF is possible using chorionic villus sampling (CVS) or amniocentesis. It is preferable that DNA testing of the parents is conducted prior to conception to determine the exact CF mutations that they may carry. This enables targeted testing for specific CF mutations in the foetus and makes interpretation of the results of these prenatal tests more specific.

CHORIONIC VILLUS SAMPLING (CVS)

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 CF mutations to determine if the foetus has CF. If the foetus is affected, the parents have a difficult choice to make; either to consider the option of terminating the pregnancy, or choosing to continue with the pregnancy with the knowledge that the baby will be born with CF. Genetic counselling to assist in this process is highly recommended. If the parents decide to continue with the pregnancy, the birth of this baby can then be planned, ensuring that the necessary medical expertise is in place. The CVS procedure carries a 2 to 3 % risk of miscarriage. An advantage of this procedure is that a CF diagnosis can be obtained early in the pregnancy if termination of the pregnancy is an option parents wish to pursue.

AMNIOCENTESIS

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

PRE-IMPLANTATION DIAGNOSIS (PGD)

Pre-implantation diagnosis (i.e. checking at the very earliest stage of embryonic development whether CF is present) is presently available in SA only at a few specialist fertility centres. Both parents must have their CF mutation status determined prior to any pregnancy attempt. Eggs and sperm are harvested from prospective parents and after in *vitro* fertilisation (IVF), the developing embryos are screened for their CF status. Only selected embryos free of CF are implanted into the womb. Prenatal diagnosis of all PGD pregnancies is recommended as PGD has a small margin of error due to technical challenges. All PGD procedures should be accompanied by careful genetic counselling, and parents need to be aware of the challenges and limitations of PGD.

Parents of a child with CF who are planning to have more children should consult with their doctor and with a genetic counsellor/geneticist before embarking on a new pregnancy.

3.3. NOVEL AND FUTURE CF THERAPIES TARGETING CFTR MUTATIONS

Since the discovery of the CFTR gene in 1989, there has been a worldwide search for drugs that target the CFTR gene with a view to restoring its function to normal levels to allow for normal electrolyte movement across the apical surface epithelium. A number of drugs have been developed targeting different mutation classes. Drugs targeting two major classes have been translated from laboratory trials to clinical practice or advanced clinical trials.

In order to understand the CFTR targeted therapies, it is important to appreciate that there are a number of classes of the CFTR mutation (Table 3.2).

Table 3.2 The basic genetic defects in CFTR according to mutational class (*Adapted from Solomon GM, Marshall SG, Ramsey BW, Rowe SM. Breakthrough therapies: cystic fibrosis (CF) potentiators and correctors. Pediatr Pulmonol 2015;50(40)S3-S13)*

Class of mutation	Basic defect	Example of mutation
Class I	Absence of gene synthesis, nonsense mutations and large deletions	621+1G→T, 3659delC, 1717-1G→A
Class II	Premature stop degradation or incomplete maturation	p.Phe508del, G85E, R506T, N1303K
Class III	Disordered regulation such as diminished ATP binding ad hydrolysis	**G551D,** S1251N, S1255P, G551S, G970R, G178R
Class IV	Defective chloride conductance or channel gating	R117H, R334W, R347P
Class V	Reduced number of CFTR transcripts due to promoter or splicing abnormality	2789+5G→A, 3849+10KcC→T, A455E
Class VI	Accelerated cell turnover from cell surface	

POTENTIATORS

Potentiators are compounds that function by attempting to restore the function and activity of the CFTR in patients with class III and similar gating mutations. These drugs increase the time that the activated CFTR channel remains open and functional. While it is postulated that those with Class IV mutations should benefit from these drugs, there is insufficient research currently for use with these mutations. Only a small number of people with CF in Europe (between 4-5%) have the class III gating mutations.

The most commonly known and studied drug in this field is Ivacaftor (formerly VX-770). This drug has been studied in a number of phase 3 and phase 4 trials in children age 6 and above who carry at least one allele of the G551D mutation. Ivacaftor has consistently been shown to improve lung function tests (FEV1% increase around 10% relative change) and quality of life scores, increase weight gain (mean 2.5kg) and are associated with significant reductions in the number of pulmonary exacerbations (55% decrease in one study). Ivacaftor has also been shown to improve biological markers like a reduction in sweat test measurements and improvement in nasal potential difference measurements. Potentiators have been studied with the most common CFTR mutation dF508.phe; unfortunately, this drug had no effect on lung functions or number of exacerbations.

CORRECTORS

The p.Phe508del mutation affects the maturation of the protein, which includes its folding and activation. The stability of the Phe508 protein is essential for activity at a number of sites.

- Stability of the nucleotide binding domain (NBD1) to prevent retention in the endoplasmic reticulum
- Facilitation of binding between the membrane spanning domain (MSD2) and NBD1. MSB2-NBD complex allow for opening of the NBD
- Prevent premature degradation and shortening of the cell surface half-life

There are several correctors, with the most well studied being Lumacaftor (VX-809). The effect of Lumacaftor is mediated by stabilising the NBD-MSGF inter-domain assembly and reducing cellular microprocessing. The effect of Lumacaftor on its own is modest on correction of the p.Phe508del mutation, but this effect is improved by 50-100% by the addition of Ivacaftor to the treatment. Therefore, Lumacaftor monotherapy (alone) is not very efficacious, showing only modest improvements in sweat tests. Corrector-potentiator therapy is the current choice of treatment. This drug combination is beneficial for patients with p.Phe508del homozygous mutations with modest improvements in FEV1 (around 2.5%), reduction in the number of exacerbations by around a third and modest improvements in body mass index. Although this combination of agents is effective, the results are much more modest when compared to those of the potentiators for gating mutations alone. The major side-effect of Lumacaftor is bronchospasm.

The other corrector VX-661 is currently under study for patients who are homozygous and heterozygous for the p.Phe508del mutation. The results from this agent have been encouraging with early phase 2 trials showing improvements in FEV% in patients with p.Phe508del /G551D mutations and p.Phe508del /p.Phe508del mutations. This agent does not cause bronchospasm.

Research involving drugs that improve the CFTR localisation and augmentation of the chloride channel are continuing and other novel gene-directed therapies are anticipated in the future.

CHAPTER 4. MAKING THE DIAGNOSIS OF CF

The classification and diagnostic criteria for CF have recently been revised and are summarised in this chapter along with diagnostic approaches.

4.1 TYPICAL OR "CLASSICAL" CF

- Phenotypical features and clinical presentations (see table 2.1), either pancreatic sufficient or insufficient
- Positive sweat test
- 2 disease-causing CFTR mutations identified. However absence of genetic confirmation does NOT exclude the diagnosis of CF in the SA context

4.2 ATYPICAL CF OR CFTR-RELATED DISORDER/DYSFUNCTION

This is a term used to categorise patients with mild, "atypical" or single organ disease who do not fit the classic CF diagnosis criteria:

- Atypical phenotypic presentations as described in Chapter 2
- Sweat chloride 30-59 mmol/L (intermediate range)
- Absence of two known CF-disease causing mutations; or presence of one or two mutations of variable clinical consequence (MVCC) or unknown clinical consequence

4.3 CHOICE OF DIAGNOSTIC TEST

The sweat test (either sweat chloride concentration or conductivity) remains the most important and frequently used clinical test for the diagnosis of CF. Conductivity tests are more readily available but are not as reliable as sweat electrolyte testing. There are different cut-off values depending on the methodology used and the age of the patient (Figure 4.1). Abnormal sweat conductivity levels should be confirmed with formal sweat electrolyte testing where possible.

Where sweat testing is not available, the faecal pancreatic elastase test is useful to demonstrate pancreatic insufficiency. Faecal pancreatic elastase levels below 100-200 micrograms/ml indicate pancreatic insufficiency. In circumstances where the pre-test probability of a CF diagnosis is high and sweat testing is not available, sending a blood sample for DNA testing is appropriate.

The following diagnostic algorithms (Figs 4.1 and 4.2) provide guidance for diagnosis of CF in the SA context.

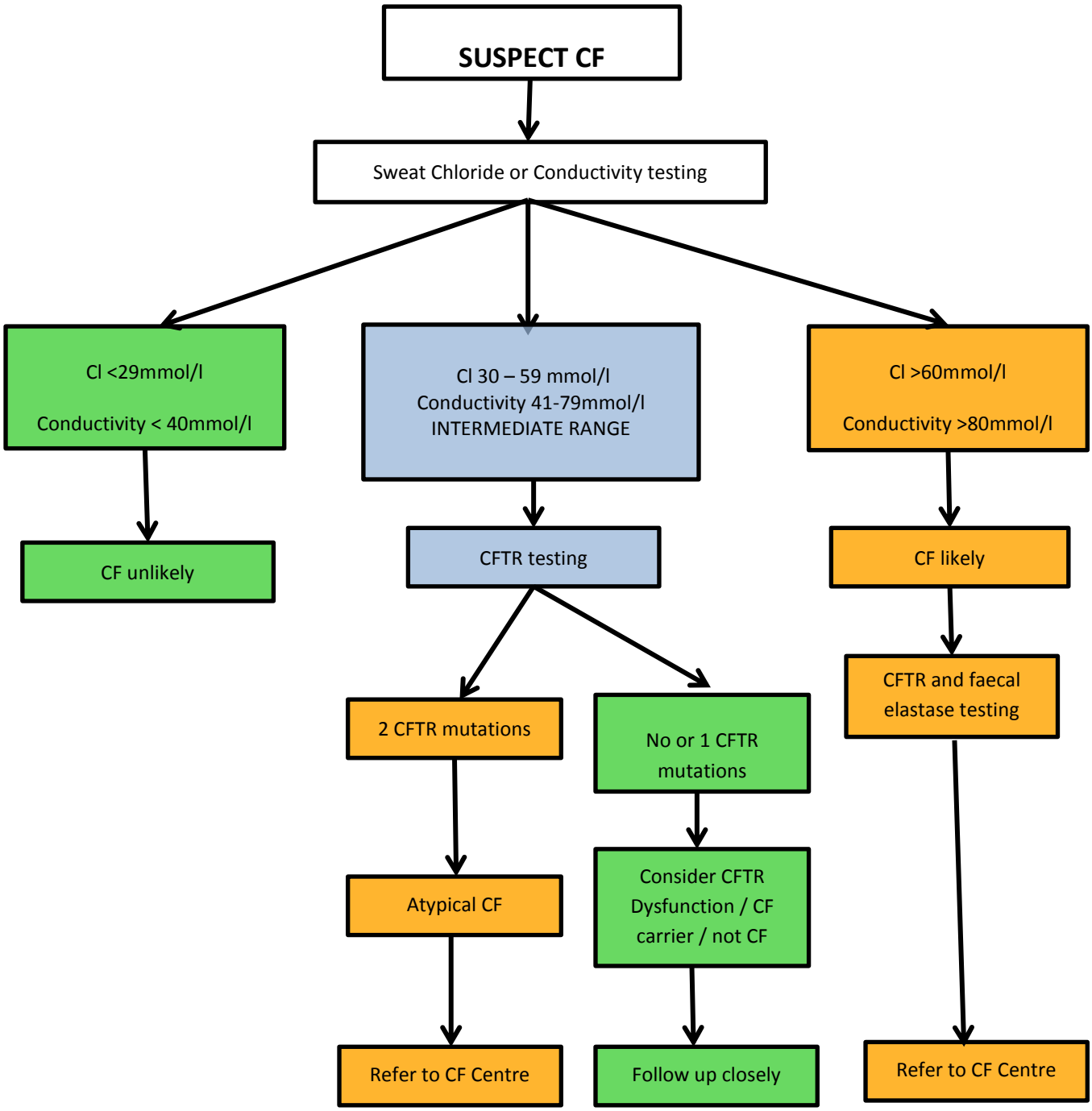

FIGURE 4.1: RECOMMENDED DIAGNOSTIC ALGORITHM FOR CF IN SOUTH AFRICA

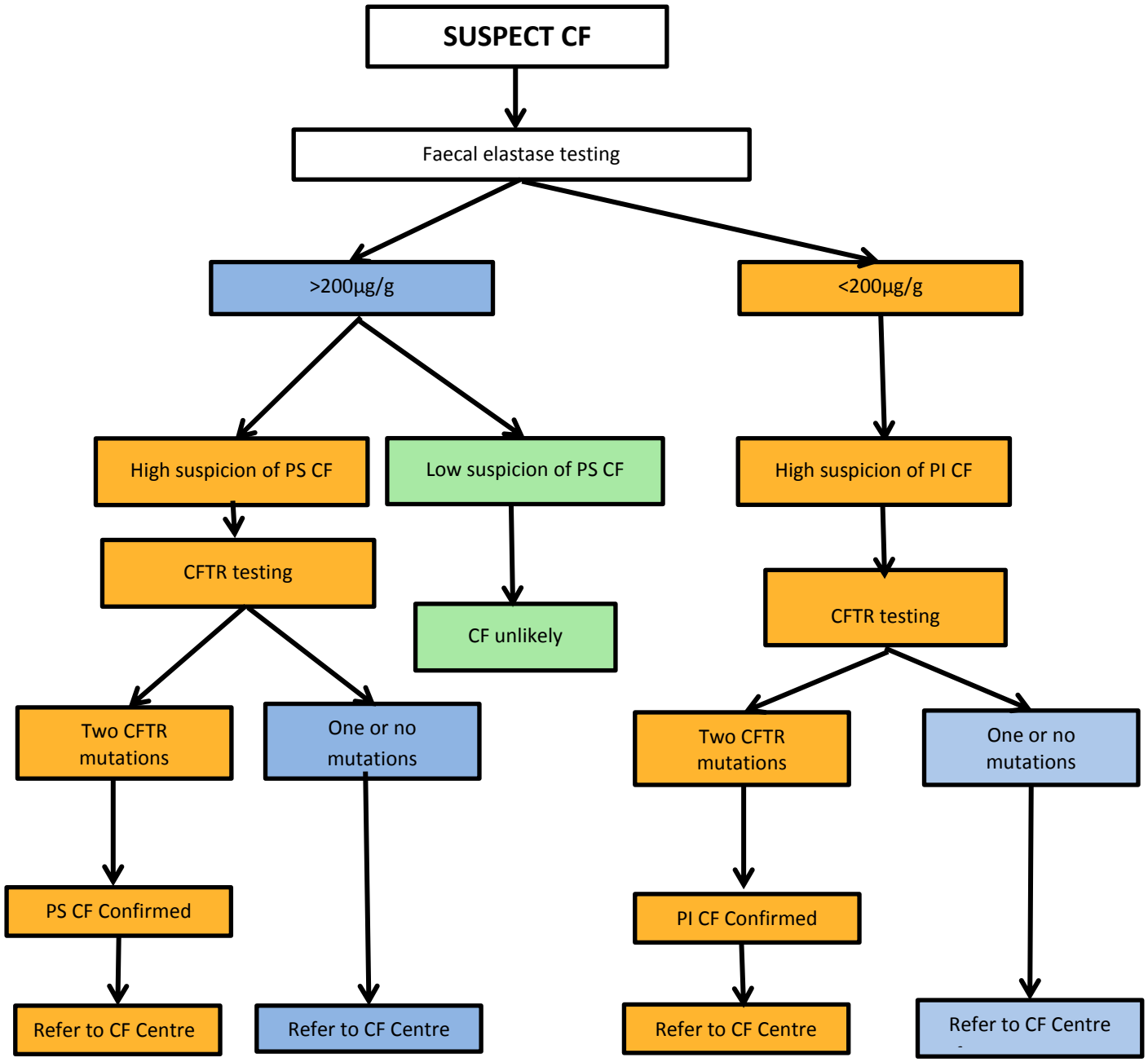

FIGURE 4.2. RECOMMENDED DIAGNOSTIC ALGORITHM WHERE SWEAT TESTING IS NOT AVAILABLE. * *Male infertility due to CBAVD, chronic or recurrent pancreatitis, ABPA, mild isolated bronchiectasis, diffuse panbronchiolitis, neonatal hypertrypsinoginaemia. severe recurrent sinusitis or nasal polyposis, sclerosing cholangitis.*

Two positive sweat tests measuring chloride concentration (performed by laboratory personnel experienced in the technique) should be done before a definitive diagnosis of CF is made. Sweat conductivity test is a useful screening tool, but is not a diagnostic test. Repeat sweat testing at a later stage should be considered in the absence of CFTR mutations. It is advised that all people with CF have CFTR testing as this has potential therapeutic and prognostic implications.

The diagnosis of CF may be inconclusive, and false positives and negative results are possible. Referral to CF Centres or discussion with CF experts is advised in these circumstances. Repeat testing may be required.

CHAPTER 5. GENERAL MANAGEMENT AND PACKAGE OF CARE

The outlook for people with CF has improved significantly. Many of the clinical features previously thought to be inevitable can be prevented, delayed or improved by intensive treatment and early intervention. The introduction of a more positive attitude to management and the more widespread use of aggressive treatment regimens have been major factors in improving longevity and quality of life.

5.1. COMMUNICATION AT THE TIME OF DIAGNOSIS

It is often difficult for parents and/or patients to fully comprehend the news when a diagnosis of CF is first made and explained, owing to the complexity of the disorder and the inevitable high levels of anxiety. Information received at the time of diagnosis should therefore be reinforced at subsequent visits.

Information about CF should be communicated to general practitioners, caregivers, teachers, relatives and friends, where appropriate. For additional information, patients and their families should be referred to reputable websites, as information on the internet is not peer reviewed and may be incorrect and/or inappropriate. It may be helpful for relatives to talk to the families of other affected individuals. Mutual support is often beneficial.

Ideally, patients should be introduced or referred to all members of the MDT soon after diagnosis. The following should be discussed with the patient and/or family around the time of diagnosis:

- CF remains a serious disorder despite the major advances of recent years
- Provide an overview of what CF is and the spectrum of disease presentation
- Potential complications and long-term expectations
- The necessity of adherence to prescribed treatments
- Long-term health and prognosis is largely determined by early childhood factors, therefore attention to attaining normal child health is critical
- Routine immunisations are essential, with the addition of annual influenza and varicella vaccinations. Where available, palivizumab (Synagis®) should be considered in infants to protect against respiratory syncytial virus (RSV) infection
- Smoking, both active and passive, should be actively discouraged and active smokers in the household of the person with CF should be referred to smoking cessation programs
- Where possible, close contact with people with respiratory tract infections (including the common cold) should be avoided to prevent cross-infection
- CF is a complex disorder and advances in treatment occur rapidly. Therefore, all people with CF must be cared for under the guidance of a CF specialist team
- The hereditary aspects of CF must be discussed, to ensure appropriate family planning choices are made from the outset. Referral to a genetic counsellor is recommended.
- Families should be informed about the Cystic Fibrosis Association (Appendix C)

5.2 RECOMMENDATIONS FOR MINIMUM STANDARDS OF CARE FOR CF IN SOUTH AFRICA

A centralised MDT approach is considered the preferred model to deliver CF care. This approach improves quality of life and CF life expectancy.

This section describes minimum standards of care for CF that are relevant to the SA setting, with its inherent inequalities between public and private healthcare systems. Further it sets out accreditation criteria for specialised CF clinics to provide a stratified system for the country based on minimum acceptable norms. By setting a benchmark for the minimum requirements for CF services, it is hoped that all CF patients will have equitable access to specialised MDT care.

RECOMMENDATIONS FOR BASIC PACKAGE OF ROUTINE CARE THAT SHOULD BE OFFERED BY CF CENTRES FOR CHILDREN AND ADULTS

FREQUENCY OF VISITS:

Patients should be reviewed regularly with a frequency appropriate to their individual needs, but must ideally be seen at least 3-4 times a year by a designated MDT CF centre. Patients without easy or frequent access to a MDT CF centre should be seen at least once a year with interim shared care between the CF centre and the local healthcare provider/s. Infants and newly diagnosed people should initially be seen more frequently.

Routine systematic evaluation at each routine visit

a) Review overall health status including new symptoms or recent illness

b) Assess family, personal and psychosocial issues, including lifestyle risk behaviours such as smoking. Evaluate school or workplace performance and progress. Regular contact with a social worker is recommended.

c) Review immunisation status in children, including annual influenza vaccine in all

d) Assess dietary intake, meal plans, bowel patterns and enzyme supplementation. Ideally should be formally assessed by a dietician.

e) Measure and monitor nutrition and/or growth (weight, height) in children and BMI in adolescents and adults.

f) Systematic physical examination with focus on upper respiratory tract (sinuses, polyps), respiratory and gastrointestinal systems.

g) Check blood pressure in those on regular oral corticosteroids and in post-transplant patients.

h) Perform lung function testing with spirometry from 5-6 years of age. Pulse oximetry should be measured in people with exacerbations or FEV1 < 40% predicted.

i) Collection and culture (including mycobacterial cultures) of sputum in all patients (oropharyngeal swabs in young children): Induced sputums should be performed in people unable to expectorate. Ensure laboratory systems are in place to process CF samples correctly.

j) Review all medications and adherence, including potential adverse events. Enquire about nebuliser usage and hygiene.

k) Enquire about reproductive health matters, family planning and pubertal development where appropriate. Adolescents should be provided an opportunity to consult without their parents.

l) Test urine for glucose if the patient has unexplained weight loss or if they are receiving oral corticosteroids.

m) Perform other appropriate investigations as indicated: e.g. chest x-ray, blood investigations etc.

Annual Review:

The annual review is a detailed assessment of every aspect of the patient's condition and therapies, to assess changes over the last year, identify where treatments can be optimised, and develop a management plan for the following year. Annual reports should ideally be generated by a CF centre once all results are available, and sent to all the relevant clinicians who are involved in the shared-care of the patient.

Additional annual investigations should include:

a) Blood tests: full blood count, clotting studies (in the case of liver disease), electrolytes and renal function, liver function tests, and vitamin A, D and E levels

b) Chest radiograph. Routine CT scan surveillance in children is not recommended in SA due to lack sufficiently equipped and trained radiology centres with capacity and expertise to perform low dose radiation CT

c) Liver and portal system ultrasound

d) Diabetes screening (OGTT and HbA1c)

e) Allergic bronchopulmonary aspergillosis (ABPA) screening with Total IgE, RAST- *Aspergillus* and/or skin prick tests for *Aspergillus* spp.

f) Bone health screening in adolescents and adults: serum calcium, alkaline phosphatase (ALP), phosphate and (parathyroid hormone (PTH). DXA scan every 1-3 years is recommended

LEVELS OF CF CARE

Prescribed models of comprehensive CF care may be difficult to implement across SA and alternative approaches may need to be adopted. Of importance is that every patient with CF should be registered with a recognised MDT CF centre and attends the centre at regular intervals. The frequency of attendance will depend on individual circumstances and need, including geographical location and whether the patient predominantly uses private or public healthcare systems.

- Level 1, 2 and 3: see table 5.1 for explanations
- *Public sector patients:* All newly diagnosed patients with CF must be discussed with and referred to the nearest MDT CF centre (Level 2 or 3, usually based at a tertiary hospital). Depending on the patient's geographical location, routine CF care is offered either exclusively by the CF centre, or care is shared with the nearest appropriate healthcare facility at regional or district level. Suitable travel and transport arrangements should be put in place to facilitate attendance at the CF centre
- *Private sector patients*: All newly diagnosed or known patients with CF should be referred to the nearest public or private sector recognised Level 2 or 3 CF centre or practice. Shared-care arrangements between public-private, or private-private care providers need to be established and maintained with regular communication

TABLE 5.1 LEVELS OF CF CARE RECOMMENDED FOR SA

Level	Staffing/Practitioners	Infrastructure	Investigation capacity/equipment	Visit frequency	Requirements/ Other services
1	• Individual practitioners – General practitioner (rural or remote regions) – Senior Medical Officer (public sector) – Paediatrician (all children) – Pulmonologist/physician (adults) • ***Ideally should be caring for 10 or more patients with CF***	• Consulting rooms or clinic • Public or Private sector	• Access to routine haematology, chemistry and microbiology laboratory services • A link to a reference laboratory services is recommended • Mechanisms to review and act on all laboratory investigations e.g. sputum cultures	• Unlimited	• ***Shared-care with level 3 (or level 2 when level 3 not feasible) is essential. All new patients with CF to be referred to Level 2/3*** • Unlimited access to a CF expert/medical practitioner at Level 2 or 3 • Capacity and facilities to admit patients with CF and supervise these admissions • Capacity to supervise home-based IV therapy including maintenance of ports is recommended, but not essential • Access to pharmacy services capable of supplying all essential CF medications and therapies
2	• At least one recognised adult or paediatric CF expert/ specialist/sub-specialist	General paediatric clinic • Consulting rooms	• Access to routine haematology, chemistry and microbiology laboratory services. A link to a reference laboratory is recommended	• Unlimited but ***minimum 3 per annum***	• ***Must refer all new and known patients with CF to Level 3 (where feasible) at least once per annum***

	– *Public sector Level 2/ Regional Hospital* ▪ Paediatrician (children) ▪ Physician (adults) – *Private sector* ▪ Pulmonologist (paediatric or adult) ▪ Accredited non-specialist CF expert (public or private) • Access to a dietician with knowledge of CF • Access to a physiotherapist with knowledge of CF		• Mechanisms to review and act on all laboratory investigations e.g. sputum cultures • Access to routine radiology (x-rays, ultrasound and CT scan) • Access to reliable CF diagnostic testing i.e. sweat test and/or molecular genetics laboratory • Capacity to perform reliable spirometry in children (> 5 years) and adults at every consultation or visit • Spirometry must be performed by a suitably trained individual		• ***May assume Level 3 role in circumstances where access to Level 3 care is not feasible e.g. rural or underserviced region*** • Capacity and facilities to admit patients with CF and supervise admissions • Capacity to supervise home-based IV therapy including maintenance of ports is recommended • Access to pharmacy services capable of supplying all essential CF medications and therapies • Must adhere to basic infection-control measures related to CF care • Capacity and willingness to participate or contribute to CF-related training and research • Access to a computer with internet access at the site of clinical service

3	• At least one recognised adult or paediatric CF expert/ specialist/sub-specialist • Two or more full or part-time CF experts are recommended for a service with 40 or more CF patients • Access to after-hour consultation with a CF specialist is required • Access to a range of adult or paediatric sub-specialists including pulmonologists, gastroenterologists, endocrinologists, general and thoracic surgeons • Access at all times to a dietician with knowledge of CF • Access at all times to a physiotherapist with knowledge of CF • Access to other MDT professionals including social	• CF clinic/ outpatient facility • Consulting rooms	• Access to routine haematology, chemistry and microbiology laboratory services • A link to a reference laboratory services is required • Mechanisms to review and act on all laboratory investigations e.g. sputum cultures • Access to routine and specialised radiology (e.g. x-rays, ultrasound and CT scan, DXA scans) and other investigations, e.g. endoscopy • Access to reliable CF diagnostic testing i.e. sweat test and/or molecular genetics laboratory • Capacity to perform reliable spirometry in children (> 5 years) and adults at every consultation or visit • Spirometry must be performed by a suitably trained individual or accredited pulmonary function laboratory	• Unlimited but ***minimum 1 MDT clinic attendance per annum***	• ***20 or more CF patients registered*** • Capacity and facilities to admit patients with CF and supervise CF admissions • Capacity to supervise home-based IV therapy including maintenance of ports is essential • Access to pharmacy services capable of supplying all essential CF medications and therapies • Must adhere to basic infection-control measures related to CF care • Capacity and willingness to participate or contribute to CF–related training and research • Access to a computer with internet access at the site of clinical service

	worker, genetic counsellor and psychologist • Adequate administrative/ clerical support staff appropriate for the size of the clinical service • Adequate nursing staff appropriate for the size of the clinical service • The service of a CF clinical nurse practitioner is recommended for the larger CF centres				

CHAPTER 6. RESPIRATORY MANIFESTATIONS AND PULMONARY CARE

6.1 INTRODUCTION AND OVERVIEW

Lung disease is the primary cause of morbidity and death in people with CF. 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*.

6.2 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 deteriorating lung function, progressive lung disease and infections may delay or prevent irreversible structural lung damage.

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 the 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.

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 monitoring response to treatments. The standard flow-volume parameters FEV1 and FVC are the most useful, but have limitations. Despite optimal treatment, a rate of FEV1 decline of 1-2% per annum is expected. Early changes of peripheral airway obstruction may be detected by reductions in FEF25-75. Any decline in pulmonary function should be evaluated in the context of the individual patient and not that of the population norms.

Spirometry is reliable 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. Newer modalities such as lung clearance index (LCI) and Forced Oscillatory Technique (FOT) measure different aspects of pulmonary function and are becoming commercially more available. Interpretation of these tests requires caution as normative values are not yet established. The advantage of these modalities is they are performed with tidal breathing and are therefore possible in young children, without the need for cooperation. LCI is also more sensitive than spirometry at detecting early lung disease.

SPUTUM MICROBIOLOGICAL SURVEILLANCE

Regular (3-4 monthly) monitoring of respiratory tract cultures is important 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 voluntarily. Oropharyngeal or cough swabs should routinely be performed in young children even if asymptomatic. Bronchoscopy and bronchoalveolar lavage (BAL) culture is not indicated in the routine care of patients with CF but may be indicated in specific circumstances, e.g. where identifying unrecognised infections will influence antibiotic management, and when good quality sputum specimens cannot be obtained by usual methods. Annual BAL surveillance is practised in some centres in young children in study cohorts. There is, however, no evidence that this invasive approach improves outcomes.

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 gross changes or trends in lung structure or volumes. Unless clinically indicated (e.g. atelectasis, pneumothorax), frequent and repeated chest x-rays should be avoided even if patients present with repeated pulmonary exacerbations. CT scan is the most sensitive technique to monitor structural changes in the lung, especially in young children. However significant radiation exposure (especially to children) precludes CT from being useful in the routine monitoring of CF lung disease. Low-dose radiation strategies are essential if CT is used as a modality for monitoring and it is estimated that one CT scan every 3 years is safe provided standardised scoring measures are used to monitor changes.

6.3 COMMON RESPIRATORY PATHOGENS AND TREATMENT STRATEGIES

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 people with CF. 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 antibiotic therapy where certain chronic infections are established.

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 and **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 patients without pulmonary exacerbations. Other symptoms and suggestive of exacerbation are:

- Poor weight gain or loss of weight
- Change of sputum colour from white to yellow or green

- Change in sputum quantity and smell, and/or
- New infiltrates or changes on chest x-ray [Chest rays are not required to diagnose pulmonary exacerbations and should not be performed with every exacerbation]

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

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

- The severity of symptoms: Generally, mild exacerbations i.e. absence of systemic symptoms, are initially managed with **oral antibiotics (2-week course). 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.
- Bacteriology: Treatment is guided by which bacterial or other pathogens are isolated in the patient's sputum and whether or not the patient is chronically infected (colonised) with certain pathogens. 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 *Aspergill*us in the sputum from a colonised patient who is well and does not have new symptoms does not require treatment.

OVERVIEW OF CHRONIC INFECTION/COLONISATION

Although *Pseudomonas aeruginosa* remains the most important pathogen in CF-related lung disease, there is increasing recognition of a host of clinically relevant existing, emerging and novel infections. Although data from South Africa are lacking, the epidemiology of traditional CF pathogens in the United States shows temporal evolution over both the lifespan of a patient with CF, as well as an era effect (Figure 6.1).

This changing epidemiology is driven by the selective pressure of antimicrobials; the development of novel technologies for the detection and identification of microorganisms in the sputum of patients with CF; the clustering of patients in CF clinics where nosocomial transmission may occur; increased length of time living with CF; and changes in infection control practices. A few important infections and their management are discussed below:

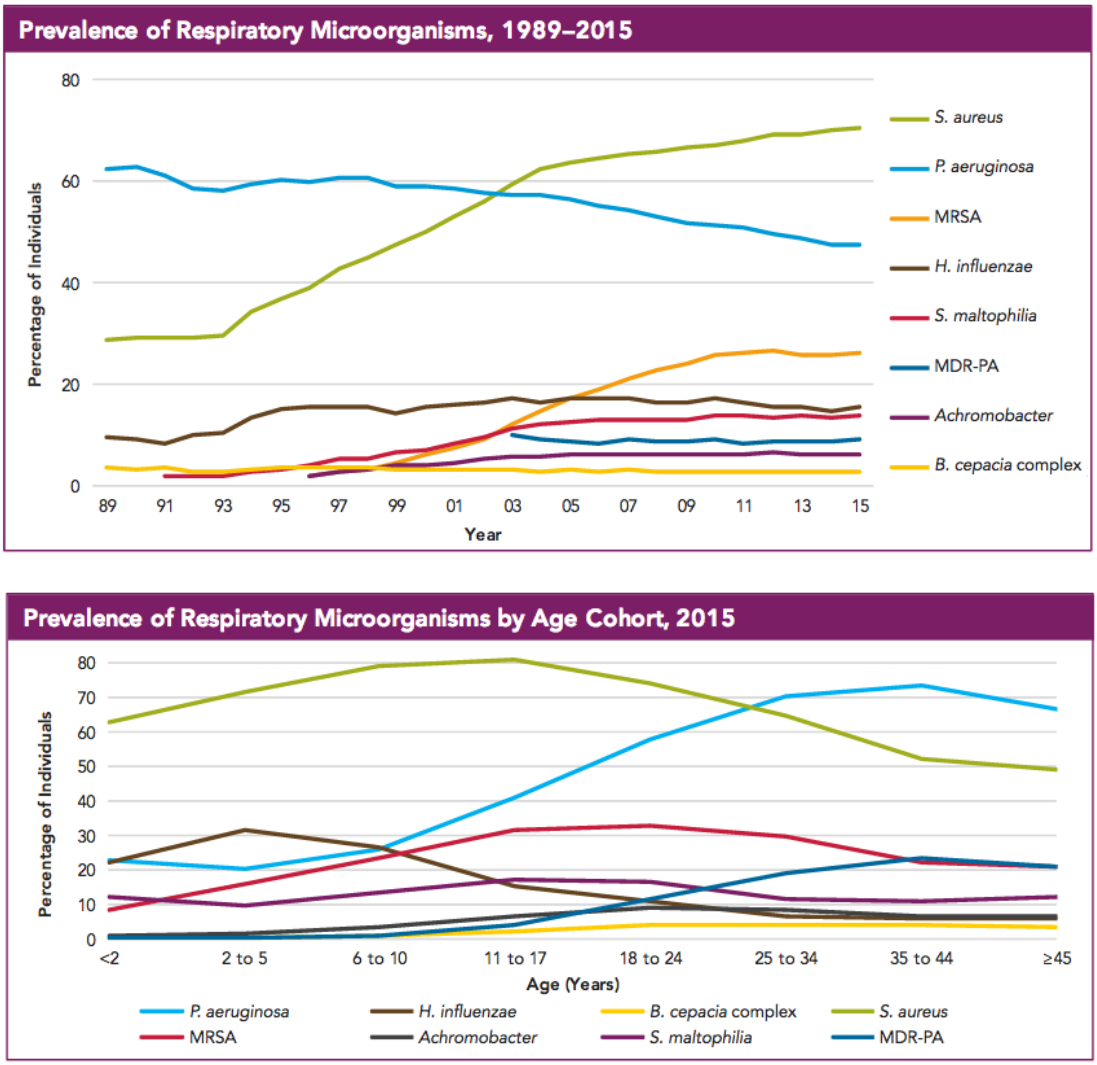

FIG 6.1: PREVALENCE OF RESPIRATORY MICROORGANISMS IN PEOPLE WITH CF IN USA (FROM CFF REGISTRY DATA 2015)

TABLE 6.1 COMMON CF-ASSOCIATED PATHOGENS:

Pathogen	Clinical significance	Management (Appendix A)
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. aeruginosa*. The risk of bacterial resistance to the antibiotic is increased with prolonged 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 or co-amoxiclavulanic acid. Alternatives: Macrolides, clindamycin, cephalosporins (1st or 2nd generation), cotrimoxazole.
		IV**:** Cloxacillin or 2nd generation cephalosporins e.g. Cefuroxime
***Methicillin resistant S. aureus* (*MRSA*)**	Recent evidence suggests that, like *Pseudomonas*, colonisation with *MRSA* is associated with poorer long term pulmonary function. Increasing prevalence worldwide is attributed to increased antibiotic usage and repeated exposure to healthcare facilities. Strict infection control measures are advised to prevent cross-infection. Family members and healthcare workers should be screened if *MRSA* is isolated from a patient.	**1st or new infection**: attempt eradication ***regardless of symptoms*** (See section 6.4.2)
		Asymptomatic colonisation: no treatment
		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. 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 reduced long-term survival.** Acquisition of *Pseudomonas* infection may be asymptomatic, particularly in young children. Initially *Pseudomonas* is non-mucoid 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 6.4.1)
		Asymptomatic or stable chronic infection/colonisation: prophylactic inhaled antibiotics (gentamycin, tobramycin, colomycine) and anti-inflammatory low-dose macrolide e.g. azithromycin.
		Exacerbations: ***Oral:*** ciprofloxacin for 2 weeks. Oral ciprofloxacin has few side effects although photosensitive skin rashes may occur. Ciprofloxacin should not be used in patients with CF who are pregnant ***IV:*** traditionally 2 antibiotics, usually a combination of an aminoglycoside plus ceftazidime or cefipime is used. ***A minimum of two weeks treatment 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 cost-effective. High doses must be administered as patients with CF tend to metabolise some drugs, including antibiotics, more rapidly than normal (see Appendix A). Improvement during a course of IV treatment can be demonstrated by performing regular respiratory function tests and carefully assessing other signs including body weight.
Multidrug-resistant (MDR) Pseudomonas aeruginosa	Frequent antibiotic use, either for prophylaxis or treatment of exacerbations, is associated with the risk of developing antibiotic resistance. However, frequent high dose antibiotic therapy is an essential part of CF management. Acquisition of *MDR Pseudomonas* may be associated with 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, colomycine) continue even if there is laboratory resistance to the antibiotic as the concentration delivered in the airway exceeds MIC levels ensuring efficacy. Anti-inflammatories e.g. low-dose macrolide e.g. azithromycin
		Exacerbations: The choice of antibiotic treatment of exacerbations is influenced by *in vitro* bacterial susceptibilities and/or prior clinical response. 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 anti-pseudomonal 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/NPA or sputum) may help avoid unnecessary antibiotics and guide management, especially if Influenza virus is suspected.	**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 or proven. - 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 crèche's or day-care facilities. **Annual Influenza vaccination** is strongly recommended.
No identified pathogen	Pulmonary exacerbations and significant lung disease does occur where no pathogen is identified through routine laboratory methods. Infection with viruses and other common organisms e.g. *S.Pneumoniae* or *Mycoplasma* and anaerobes may co-exist in CF.	The choice of antibiotic should be determined by the most likely bacterium /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.

6.4. ERADICATION OF SIGNIFICANT INFECTIONS

PSEUDOMONAS AERUGINOSA

Chronic airway infection with *Pseudomonas* is associated with 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 and choice depends on institutional preference, cost or access to medical insurance. Inhaled aminoglycoside therapy delivers very high concentrations of antibiotic into the airway without systemic absorption. Three months low-dose azithromycin (i.e. anti-inflammatory dose) may be added to the eradication regimen.

Eradication is considered successful if, despite regular 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 thereafter aims to suppress chronic *Pseudomonas* infection by long-term use of inhaled antibiotics and anti-inflammatories i.e. azithromycin. The following *Pseudomonas* eradication protocol is recommended for the South African setting (Figure 6.2):

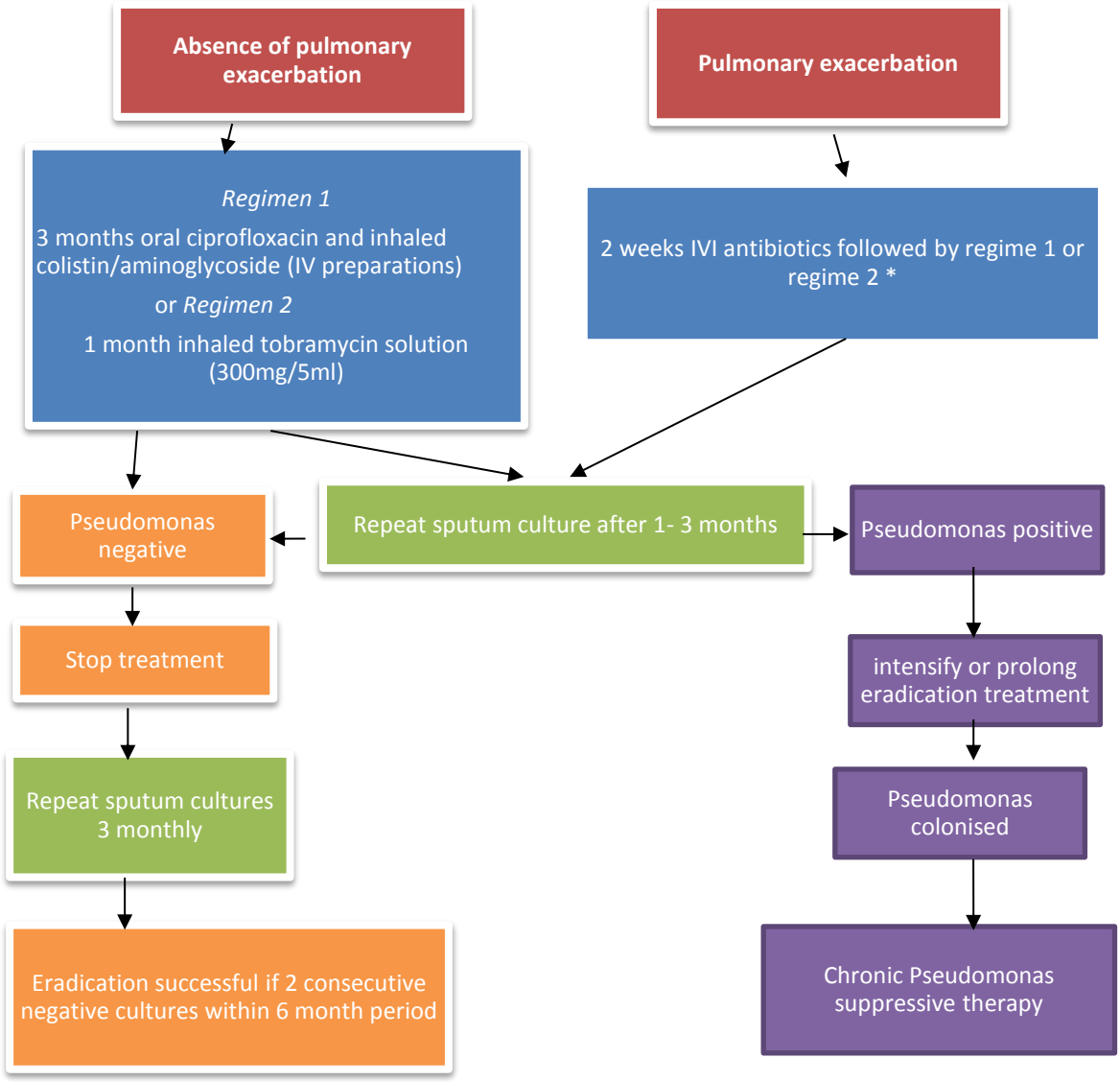

FIGURE 6.2: RECOMMENDED *PSEUDOMONAS* ERADICATION PROTOCOL FOR SOUTH AFRICAN SETTINGS

METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)

MRSA infection and colonisation is associated with worse pulmonary outcomes. Isolation of MRSA, particularly from the lower respiratory tract, should always be regarded as significant. Eradication strategies to prevent chronic infection will depend on the patient's symptoms and availability of antimicrobial agents. Several eradication protocols have been reported with anecdotal success. The following protocol, which takes these into account, is suggested for MRSA eradication in the SA context:

AT FIRST DETECTION OF MRSA ON SPUTUM/THROAT SWAB:

- Perform multi-site swabs (nose, mouth, groin, and other sites) of patient and immediate family, including nebuliser components.

- Hygiene advice should be given to patients and their parents/carers at the start of the treatment course and includes advice on changing bed linen, changing toothbrush, use of own towel, face cloth and toothbrush
- Replacement or sterilisation of all nebulisation components.
- Implement contact precautions and infection control measures during health facility/clinic visits

STEP 1: LOCAL AND SKIN DECONTAMINATION:

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

STEP 2: SYSTEMIC ANTIBIOTICS

Select at least 2 antimicrobial agents for 2-3 weeks targeting MRSA. Choice of antibiotic and route of administration depends on availability, antibiotic susceptibility patterns and symptoms:

i) Patient well, mild or no symptoms:

- Sodium fusidate 50 mg/kg/day or 500mg TDS
- Rifampicin 20–40 mg/kg/day or 300mg BD
- Cotrimoxazole 5-10 mg /kg BD or
- Linezolid 20-30 mg /kg BD

ii) Patient unwell or exacerbation**:**

- Vancomycin IV 40-60 mg/kg/day in divided doses or continuous infusion
- Intravenous teicoplanin 10–15 mg/kg/daily 12h x three doses; then 10–15 mg/kg/daily once daily for nine to 13 days

PLUS

iii) Inhaled vancomycin 50- 250 mg in 3-5 mL saline nebulised twice daily for 4-6 weeks:

STEP 3

Repeat multisite swabs and respiratory tract sampling after completing of steps 1 and 2 to ensure eradication is achieved.

6.5 UNUSUAL/EMERGING INFECTIONS

BURKHOLDERIA CEPACIA COMPLEX

The *Burkholderia cepacia* complex (BCC) is a group of gram-negative bacteria, (misclassified as a species of *Pseudomonas* until very recently) containing at least 18 different subspecies (or genomovars) of varying virulence that are now differentiated from each other by molecular techniques. Most diagnostic microbiology

laboratories are not equipped to assign genomovar designation to BCC isolates. The BCC species most commonly isolated from the sputum of patients with is *Burkholderia multivorans* (genomovar II) and *Burkholderia cenocepacia* (genomovar III). B. cenocepacia accounts for ~80% of BCC isolates from CF patients, and is particularly important because it is:

- *Associated with poor clinical outcomes: a subset of patients infected with BCC succumb to the so-called "cepacia syndrome", a rapidly-progressive bacteraemic illness with cavitary pneumonia and high mortality, and colonisation with BCC is associated with a median survival half that of CF patients infected with Pseudomonas;*
- *Highly transmissible between patients with CF both within and outside hospitals, leading to outbreaks and emphasising the need for stringent infection control measures in CF care centres*

Treatment options are limited owing to high levels of resistance, either intrinsic or acquired, to many antibiotics. Trimethoprim/sulfamethoxazole has most commonly been used. Ceftazidime, meropenem and piperacillin, either alone or in combination, could be considered as alternative options. Eradication therapy on detection is controversial and its efficacy is unknown.

Infection with Burkholderia cenocepacia is considered to be a contraindication to lung transplantation in many centres as patients with pre-transplant infection with Burkholderia cenocepacia have significantly worse post-transplant survival compared to uninfected patients with CF.

NONTUBERCULOUS MYCOBACTERIA (NTM)

Structural lung disease with impaired mucociliary clearance in CF is a predisposing factor for NTM pulmonary disease, as it is in other forms of bronchiectasis. Rates of detection of NTM in CF are increasing across the world. The most common types of NTM infecting patients with CF are the *Mycobacterium avium* complex (MAC), a group of slow growing species containing *M. avium*, *M. intracellulare* and *M. chimaera*, and the *M. abscessus* complex (MABSC). NTMs are common environmental organisms, but acquisition in CF also occurs by direct transmission. This has important implications for infection control practices within CF clinics.

The diagnosis of NTM-pulmonary disease is adapted from the American Thoracic Society (ATS) criteria in non-CF patients (Table 6.2), and requires repeated isolation on multiple sputum samples with evidence of clinical, spirometric and radiological deterioration and exclusion of other causes.

TABLE 6.2: SUGGESTED CRITERIA FOR THE DIAGNOSIS OF NONTUBERCULOUS MYCOBACTERIA (NTM) DISEASE IN CF

CRITERIA FOR DIAGNOSIS OF NTM DISEASE IN CF
All 3 criteria should be met before treatment: **1.** Positive acid-fast bacilli (AFB) or mycobacterial culture on at least 2 separate occasions, from sputum or BAL. 2. At least 1 clinical, spirometric, and radiographic findings consistent with NTM infection: • Unexplained loss in lung function • Increased respiratory symptoms (cough, sputum production, dyspnoea, haemoptysis) • Constitutional symptoms such as fever, fatigue, night sweats, or weight loss • Progression of radiographic features consistent with NTM infection (cavitary disease, single or multiple nodules, tree-in-bud opacities, parenchymal consolidation) 3. Exclusion of other comorbidities common in CF, including adequate treatment of: • Co-infections, such as *P. aeruginosa* and *S. aureus* • Mucus plugging • Nutritional deficiencies • CF-related diabetes • Reactive airway disease and ABPA • CF sinus disease

The management of NTM-pulmonary disease is challenging, and there is a limited evidence base. The United States CF Foundation and the European CF Society have recently published a joint consensus statement on the management of NTM-pulmonary disease in CF. Treatment usually involves weeks to months of intravenous antibiotics, and months to years of multiple inhaled and oral antibiotics. Side effects and toxicities are common and may limit treatment options. A summary of the guideline recommendations for the treatment for MAC and MABSC are shown below (Table 6.3):

TABLE 6.3: SUMMARY OF RECOMMENDATIONS FOR THE TREATMENT OF NTM PULMONARY DISEASE

NTM type	Treatment approach
MAC	• Daily oral antibiotic regimen containing a macrolide* (preferably azithromycin), rifampicin and ethambutol • An initial course of intravenous amikacin is recommended in cavitatory disease. * If clarithromycin-sensitive.
MABSC	• **Intensive phase** (3-12 weeks depending on clinical response): Daily oral macrolide (preferably azithromycin) in conjunction with intravenous amikacin and one or more of the following (guided by but not dictated by drug sensitivity testing, DST): - intravenous tigecycline - imipenem - cefoxitin • **Continuation phase** (12-18 months – possibly life-long): Daily oral macrolide (preferably azithromycin) and inhaled amikacin, in conjunction with 2–3 of the following additional oral antibiotics ((guided but not dictated by DST): - minocycline - clofazimine - moxifloxacin - linezolid

Individuals receiving azithromycin as part of their CF medical regimen who have a positive NTM culture should not continue azithromycin treatment while evaluation for NTM disease is underway as azithromycin monotherapy may lead to resistance.

Infection with MABSC is particularly relevant in patients undergoing lung transplantation, where it can be associated with difficult-to-treat surgical and soft-tissue infections. Persistent MABSC (or indeed, persistent MAC) is a relative (but not absolute) contraindication to lung transplantation

ACHROMOBACTER SPP.

Achromobacter spp. are aerobic, non-lactose fermenting Gram-negative bacilli similar to *Pseudomonas aeruginosa* that are widely distributed in nature, but are rare opportunistic pathogens. *Achromobacter xylosoxidans* and *Achromobacter ruhlandii* are uncommonly observed in CF populations, with a prevalence that may be increasing but is still less than 10%. Isolation of *A. xylosoxidans* poses a diagnostic challenge; isolates are not infrequently incorrectly identified as *B. cenocepacia* or *P. aeruginosa*. Risk factors for acquisition of *Achromobacter* spp. are largely unknown, but may include older age, increased burden of structural lung disease and chronic *P. aeruginosa* infection. *Achromobacter* infection is associated with worse radiographic and spirometric measures of lung disease. It can be the dominant, and sometimes only, bacterium isolated from patients with CF at end stage. Antibiotic resistance is common, and limits treatment options: the antibiotics most likely to have activity include the carbapenems, piperacillin/tazobactam and tigecycline. Many isolates are also susceptible to high-dose inhaled colistin. There are no data on optimal treatment of *Achromobacter* spp. in CF for pulmonary exacerbations, new colonisation or chronic infection, and treatment should be guided by the results of antibiotic resistance testing.

STENOTROPHOMONAS MALTOPHILIA

Stenotrophomonas maltophilia is a rod shaped, aerobic, non-fermenting gram-negative bacterium which is usually implicated in nosocomial or ventilator-associated pneumonia. Most incident *S. maltophilia* isolates appear to be transient colonisers; persistent infection only occurs in the minority of cases, and is driven by the use of antipseudomonal antibiotics (fluoroquinolones, in particular). It is particularly common among adolescents and young adults with CF. There is conflicting data regarding clinical significance, but *S. maltophilia* colonisation may be associated with more frequent pulmonary exacerbations, and an increased risk of death or need for transplantation. Intrinsic antibiotic resistance is a characteristic of *S. maltophilia*, and isolates from patients with CF may be even more resistant than non-CF isolates. Susceptible antibiotics may include trimethoprim-sulfamethoxazole, tigecycline, doxycycline, levofloxacin and ticarcillin-clavulinic acid. Combination therapy during a pulmonary exacerbation has been advocated but data is lacking.

FUNGAL INFECTIONS

Improved methods to recover fungi from the airways of patients have led to increasing recognition of their role in the microbiome of the CF lung. Fungi can be isolated from ~80% of CF sputum samples when fungal-selective culture methods are used, compared to ~20% of samples when only conventional non-selective media are used. Polymerase chain reaction (PCR)-based techniques are even more sensitive, and it is becoming increasingly clear that the prevalence of fungal colonisation in CF has been grossly underestimated. Culture-based studies show the most commonly isolated fungus by far is *Aspergillus fumgatus*, which can be present in ~50% of patients. Other fungi include *Scedosporium* spp., *Cladosporium* spp. and *Candida.* However, the pathogenicity of these fungi and yeasts, and their epidemiological association with the progression of CF lung disease remains unclear. Fungal colonisation may simply be a consequence of more antibiotic use and more frequent exacerbations, and *Aspergillus* colonisation may be a marker of more severe lung disease.

The most well recognised clinical syndrome resulting from fungal colonisation of the airways is allergic bronchopulmonary aspergillosis (ABPA). The effect of *A. fumigatus* in the airways of patients with CF and in the

absence of ABPA – also referred to as *Aspergillus* bronchitis - is largely unknown. Small studies suggest that it may be associated with lower forced expiratory volume in one second (FEV_1) and increased risk of pulmonary exacerbations requiring hospitalisation in children. The role of intraconazole in the treatment of *Aspergillus* bronchitis is unclear.

6.6 MANAGEMENT OF CHRONIC AIRWAY INFECTION AND INFLAMMATION

ANTIBIOTICS

PERIODIC OR PLANNED INTRAVENOUS ANTIBIOTICS

Periodic or planned hospitalisations for treatment with intravenous antibiotics every three to four months, often referred to as a "tune up" or a "clean out", has been common practice in some CF centres. There is little evidence to support this practice. As well as the high cost of such treatment and the disruption to patients' daily lives, frequent use of intravenous antibiotics will prematurely select multidrug-resistant organisms, making treatment of inevitable acute exacerbations more problematic. However, periodic hospitalisation may be justified in adolescents with poor adherence and in cases with socioeconomic and other circumstances resulting in suboptimal outpatient care.

AEROSOLISED ANTIBIOTICS

Aerosolised antibiotics directed against *Pseudomonas aeruginosa* are an important strategy for suppression of chronic infection in CF. The rationale for inhaling antibiotics is to maximise drug delivery to the target site of infection (the airways) and to limit the potential for systemic side effects. Antibiotic resistance as measured by *in vitro* susceptibility testing does not preclude a response to inhaled medications. Aerosolised antibiotics may reach maximal drug concentrations in the airways several-fold higher than can be achieved by intravenous administration, and may easily exceed the minimum inhibitory concentration (MIC) breakpoints required to inhibit bacterial growth. Inhaled antibiotics should be administered after sputum clearance.

Regarding choice of antibiotic, the best evidence in CF is for inhaled tobramycin. The dosage of tobramycin varies in studies but the majority of trials used 300mg of inhalational tobramycin solution (TOBI®)|, nebulised twice daily via high efficiency nebuliser in alternating 28-day cycles. This preparation does not have preservatives and is adjusted to a pH of 6.0. A powdered form of tobramycin (TOBI® Podhaler)|, not yet available in South Africa, is also available in other countries as an 112mg dose delivered by inhaling the contents of four capsules using a specially designed device. However, these preparations are very expensive, and inhaled administration of injectable aminoglycoside drug formulations is an acceptable alternative in South Africa (amikacin, tobramycin or gentamycin, Appendix A). The injectable preparations may not be tolerated by patients due to hyperosmolarity and added preservatives, which may induce bronchial irritation and bronchospasm. A test dose under supervision with pre-and-post-dose spirometry or clinical observation is recommended.

Other drugs which may be given by the inhaled route for chronic suppression of *P. aeruginosa* include aztreonam lysine (a monobactam) and colistin (a polymyxin). Few studies have compared the effectiveness of different inhaled antibiotics. Colistin inhalation solution has proven efficacy but might be inferior compared with tobramycin treatment. It is a treatment option for patients with multiresistant organisms, those who do not tolerate or do not benefit from amikacin/tobramycin/gentamycin, and those experiencing deterioration between other inhaled antibiotic cycles.

INTRAVENOUS ANTIBIOTICS AND VENOUS ACCESS

HOSPITAL INTRAVENOUS (IV) 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
- Physiotherapy
- Psychosocial evaluation and intervention

The duration of a course IV therapy varies but must *not be less than two weeks* (See Table 6.1 and Appendix A). Repeat clinical and pulmonary function assessment after the hospital admission should be done to demonstrate any beneficial effect.

HOME IV ANTIBIOTIC THERAPY

Many studies have demonstrated that adequately supervised home IV antibiotic treatment is a practical, effective and acceptable alternative to hospital treatment for many people with CF. 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 regularly. At the end of the two-week course of home IV antibiotics, the patient should be reviewed to establish treatment response.

Simple, portable infusion pumps make ambulatory home and school-based IV therapy practical. Totally Implantable Venous Access Devices (TIVADs) (e.g. Port A Cath® or Implantofix®, Braun®) have also 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.

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, such as peripherally inserted long lines (PICC lines) are advised. 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.

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.

COMPLICATIONS OF TIVADS (PORTS)

The major concern is the introduction of infection which may lead to septicaemia or even endocarditis. Absolute aseptic precautions are required when accessing and using the port. A port infection is usually recognised 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 after attempting to draw blood for culture. Peripheral blood cultures should also be taken. The port should be removed at the earliest opportunity and the outlet cannula sent for culture. It is advisable to wait 2 weeks 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 1 in 1 000u 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 superior vena cava syndrome
- 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 recognised 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 patients with CF and their convenience and ease of use outweighs any disadvantages. A port enables a person with CF to readily have home based intravenous antibiotics with the least disruption to their lives as possible.

6.7 ANTIBIOTIC ALLERGIES AND HYPERSENSITIVITIES

Hypersensitivity to antibiotics can occur with any antibiotic at any time i.e. even after recurrent prior exposure. Treatment of pulmonary infections can be problematic in the face of combined drug resistance and hypersensitivity. Such reactions usually take the form of skin rashes which may range from mild erythematous reactions to Stevens Johnson Syndrome. Angio-oedema, interstitial nephritis and rarely anaphylaxis may also occur.

When a reaction has previously occurred, the offending drug should generally be avoided. In the event of resistance, when the offending drug is the only drug available to effectively treat an infection, it may be necessary to consider using that agent with a desensitisation regimen. Unless contraindicated because of previous Stevens Johnson Syndrome, desensitisation is safe and effective and should be attempted according to standard protocols in an intensive care unit setting.

DESENSITISATION REGIMEN – FOR CONTINUOUS INFUSIONS

From 24 hours before treatment, to the end of treatment, patients should be on H1 and H2 receptor blockers i.e. cetirizine 20mg bd po and ranitidine 600mg bd po. Oral or intravenous corticosteroids may also be given and the dose can generally be tapered during the antibiotic course.

Patients being treated on an antibiotic that they are allergic to, should have a minimum of the first 48 hours of IV antibiotics administered in hospital. Should the antibiotic course be completed as an outpatient, the patient should be provided with an adrenalin pen and instructions on when and how to use it. Desensitisation regimes are described in Table 6.4

TABLE 6.4 ADULT DESENSITISATION REGIMES

	PIPERACILLIN/TAZOBACTAM (adult doses)
1st dose	100mg over 6 hours
2nd dose	500mg over 6 hours
3rd dose	2g over 6 hours
4th dose	4.5g over 6 hours
5th dose	Loading dose of 4.5g over 1 hour
6th dose	9g every 12 hours run as a continuous infusion or 18g every 24 hours run as a continuous infusion x 14/7
	CEFTAZADINE AND CEFEPIME (adult doses)
1st dose	50mg over 6 hours
2nd dose	250mg over 6 hours
3rd dose	1g over 6 hours
4th dose	2g over 6 hours
5th dose	loading dose of 2g over 1 hour
6th dose	2g 8 hourly infused over 8 hours x 14/7 (Paediatric dose: 100mg/kg/24 hrs)

6.8 ANTI-INFLAMMATORY THERAPIES

MACROLIDES

Macrolide antibiotics have diverse biological effects that modulate inflammation, which are unrelated to their antimicrobial properties. In chronic *P. aeruginosa* infection, they also interfere with quorum sensing and biofilm formation, which is one of the main mechanisms by which the bacterium avoids being killed by traditional antipseudomonal antibiotics (Figure 6.3).

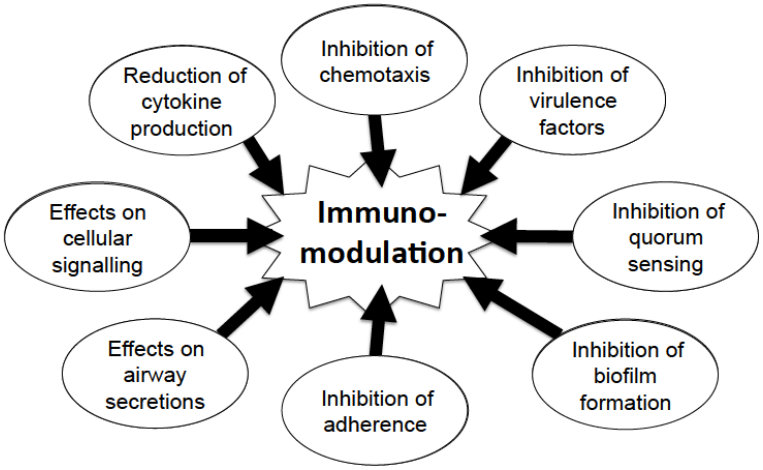

FIGURE 6.3: MACROLIDE MECHANISMS OF ACTION

Several studies have confirmed significant reductions (≥40%) in the incidence of acute pulmonary exacerbations in patients with chronic *P. aeruginosa* colonisation, and improvements in weight gain and lung function with the use of three-times-weekly azithromycin. This practice has therefore been widely endorsed in CF guidelines.

More recently, similar benefits have also been observed in patients without *P. aeruginosa*, although the magnitude of benefit appears to be smaller. The current recommendation is to prescribe azithromycin in all patients with CF older than six years of age - regardless of *P. aeruginosa* infection status – although many clinicians will reserve its use for patients who have clinical evidence of airway inflammation such as chronic cough, or who have any reduction in FEV_1. Azithromycin should be prescribed three times a week: 250mg/day for patients with body weight less than 40kg, and 500mg/day for those over 40kg.

Because azithromycin monotherapy could lead to resistance and complicate treatment in patients with occult or active nontuberculous mycobacteria (NTM) infection, patients should be screened for NTM prior to initiation of azithromycin.

SYSTEMIC GLUCOCORTICOIDS

Systemic corticosteroids are potent anti-inflammatories and can improve lung function, but there are clinically significant adverse effects with prolonged use, particularly in children. These include hyperglycaemia, bone mineralisation, linear growth retardation and appetite changes. The routine chronic use of oral corticosteroids in the absence of asthma or allergic bronchopulmonary aspergillosis in children is therefore not recommended. There is insufficient evidence to inform their use in adults, but the same unfavourable risk/benefit profile can be expected to apply.

INHALED GLUCOCORTICOIDS

In the absence of asthma and allergic bronchopulmonary aspergillosis, there is insufficient evidence to support the use of inhaled corticosteroids in CF, despite their theoretical effects on modulating airway inflammation. Despite low systemic absorption, inhaled steroids may impair linear growth in children and their indiscriminate use should be discouraged.

6.9 SINUSITIS AND NASAL POLYPOSIS

Although the incidence of chronic rhinosinusitis (CR) approximates 100% in people with CF, with 44 – 58 % of patients having nasal polyposis, only 10 – 20% of patients have self-reported chronic sinus symptoms. It is important to illicit the presence of nasal obstruction, post-nasal drip, nasal discharge and anosmia in CF patients. The paranasal sinuses are a well-known reservoir for *P. aeruginosa* and nasal endoscopy alone is often not sufficient to exclude chronic sinusitis, especially in patients who have not had prior surgery and where the sinuses cannot be inspected directly. Nasal endoscopy of the posterior nasal cavity is needed to assess for purulent secretions emanating from the maxillary sinus or spheno-ethmoidal recess. This can be difficult in the paediatric population. Abnormal sinus CT findings can be found in almost all patients with CF, therefore should only be done when indicated, e.g. for those with recurrent Pseudomonas infections.

INDICATIONS FOR ENDOSCOPIC SINUS SURGERY IN CHILDREN WITH CYSTIC FIBROSIS:

- Suspicion that the sinuses are a likely source of recurrent lung infections.
- If the sinuses act as a reservoir for *Pseudomonas aeruginosa*
- In symptomatic patients who have not responded to maximal medical treatment (topical and IV antibiotics) – patients with chronic facial pain, headaches, post-nasal drip, anosmia or a blocked nose
- Complicated sinusitis (intracranial or orbital complications)

Endoscopic sinus surgery has been proven to be beneficial in patients with CF to control recurrent respiratory infections related to chronic sinusitis, improving quality of life (QoL) and endoscopic scores. Surgery in this group of patients should be adapted and a standard endoscopic sinus surgery procedure will be of little benefit. The aim of surgery is to open the sinuses widely in order for topical medication to be adequately delivered to the nasal mucosa. The maxillary sinuses specifically should be widely opened to the floor of the nasal cavity (type 3 middle meatal antrostomy) to allow adequate penetration of topical nasal irrigations and topical antibiotics into the sinuses and to prevent stagnation of secretions within the maxillary sinuses. Without sinus surgery, less than 2% of nasal irrigations enter the sinuses so little is gained by nasal douching in unoperated sinuses. Regular sinus inspection and debridement under direct endoscopic guidance can be performed in the outpatient setting in older children and adults with CF.

The use of topical antibiotic solutions should be culture- directed and is useful in the management of chronic *Pseudomonas* and staphylococcal infections, with reduced CF sinus exacerbations in the post-sinus surgery patient. Antibiotic management in both acute and chronic sinusitis should always be culture based, with a recommended duration of 3 to 12 weeks in children with CR.

- Ceftazidime solution (1 gram IV Ceftazidime in 1 000ml normal saline) is stable at room temperature for 10 days and patients can irrigate (depending on age of patient and size of sinuses) using 50ml in each nostril twice daily for 5 days. Antibiotic irrigations should be continued for at least 2-4 weeks
- Low dose oral macrolides may be used long-term to treat CF-related RS and pulmonary manifestations due to its antibacterial, immunomodulatory and anti-inflammatory actions
- Topical corticosteroids are less effective in patients with CF who suffer from chronic sinusitis with nasal polyposis. An increased neutrophilic component has been proposed as a possible reason

- Allergic rhinitis should be treated according to standard guidelines, as for non-CF patients, with topical corticosteroids and oral anti-histamines during exacerbations

- Regular nasal irrigations with 0.9% saline have been shown to be effective in relieving symptoms and improving quality of life. High volume irrigation with isotonic and hypertonic saline solutions are more effective than normal saline nasal drops and sprays

6.10 CF- ASSOCIATED ASTHMA

Asthma is an inflammatory disorder of the airways characterised by recurrent, reversible airway obstruction. Asthma symptoms and test-to-test pulmonary function variability are common in people with CF. CF-associated asthma is not always eosinophilic as in non-CF asthma, and chronic *Pseudomonas aeruginosa* infection can be associated with a predominant Th2 immune response and symptoms of asthma.

Reversibility (≥12% increase in FEV1 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. Heterozygous carriers of CF have a higher risk of asthma than non-carriers and this be addressed in families of people with CF. The management of asthma in patients with CF follows standard asthma treatment guidelines (http://www.ginasthma.org).

Specific recommendations in managing CF-associated asthma or recurrent wheeze:

- **Mild or intermittent symptoms only**: use intermittent (as required) inhaled short-acting β2-agonists (SABA) (e.g. salbutamol, fenoterol)

- **Persistent /severe uncontrolled symptoms**: Regular low dose inhaled corticosteroids (ICS) (100-200mg daily budesonide or equivalent) plus as-needed SABA. *Other options include*:

    - Leukotriene receptor antagonists (LTRA) are generally less effective than ICS, but may be considered in atopic patients with CF, together with an anti-histamine and/or nasal corticosteroid

    - Combining low dose ICS and long acting β2-agonists (LABA) leads to faster improvement in symptoms and FEV1 than ICS alone, but is more expensive and the exacerbation rate is similar. Only use combination LABA/ICS for maintenance and in children >6 years of age

    - Medium dose (200ug budesonide equivalent daily) or high dose (400ug) ICS in children (6–11 years);

    - Low dose ICS/LABA plus extra controller, e.g. LTRA or slow-release theophylline in adults and children older than 6 years

    - Add-on treatments include tiotropium by mist inhaler for patients with a history of exacerbations (age ≥12 years)

    - Biologicals: omalizumab (anti-IgE) for severe allergic asthma, and mepolizumab (anti-IL5) for severe eosinophilic asthma (age ≥12 years) should be considered in severe uncontrolled asthma where other CF-related causes of symptoms have been excluded such as ABPA. Sputum-guided treatment, if available, improves outcomes

PRACTICE POINTS

- The preferred delivery device is a pressurised metered dose inhaler (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 under 4 years of age

- Nebulised corticosteroid or bronchodilator therapy should be discouraged as it is less effective than using MDIs with spacers, and is more 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 administration of inhaled mucolytics*, routine chest physiotherapy, and nebulised antibiotics

- Always consider alternate diagnoses in patients with CF presenting with "uncontrolled asthma", after assuring good compliance and inhaler technique. Specifically consider: allergic bronchopulmonary aspergillosis (ABPA), gastro-oesophageal reflux (GOR) and adverse effects of inhaled therapies like antibiotics or hypertonic saline

6.11. ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

ABPA is a T-helper 2, IgE-mediated hypersensitivity reaction that occurs in response to exposure to *Aspergillus fumigatus* and its 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 bronchiectasis, fibrosis and further respiratory compromise.

Up to 57% of patients with CF are colonised with *Aspergillus fumigatus,* however a positive sputum culture is not reliably linked to the development of ABPA. ABPA prevalence ranges from 1.4% to 17.9%, owing to the challenge in making a definitive diagnosis and the poor specificity of the individual components used in diagnosis. The prevalence seems to increase up until age 20, and thereafter declines.

Although ABPA is difficult to diagnose in CF patients, identification and treatment of the disease may result in improvement in symptoms and pulmonary function.

Suspect ABPA clinically if there is:

- Increased respiratory symptoms (e.g. wheeze, chest tightness, pleuritic chest pain, audible pleural rub)

- Sharp decline in spirometry without explanation

- 1 or >1 new opacities on chest x-ray. Mucocoeles, central bronchiectasis or "finger-in-glove" mucous impaction on CT chest

Annual screening for *Aspergillus* sensitisation and ABPA is recommended in individuals > 6 years of age:

- Measure total serum IgE and *Aspergillus* –specific IgE (RAST) or

- Annual skin prick test to *Aspergillus*

The following are consensus diagnostic criteria for a classic case of ABPA:

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 >2 400ng/mL or 500 IU/mL (unless the patient is on steroids in which case the patient should be tested when off steroids. Look for abrupt increase in levels, 4-fold rise)
3. Evidence of sensitisation *to Aspergillus fumigatus:* ie 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/CT chest (infiltrates or mucus plugging) that do not clear with antibiotics and physiotherapy

MANAGEMENT:

Treatment is with oral corticosteroids (prednisolone). A suggested regimen is 6-12 weeks of tapering doses of prednisolone as follows:

- First 2-4 weeks 2mg/kg/day (max 60mg/day);
- 2nd two weeks 1mg/kg/day (max 25mg/day);
- 3rd two weeks 1mg/kg alternate days and stop

An alternative regime is intravenous corticosteroids (pulsed methyl prednisolone):

- 500 mg/m^2 daily for 3 days
- Repeat every 4 weeks until clinical and laboratory resolution of ABPA

Antifungals may be used as adjunctive therapy (e.g. itroconazole, voriconazole) in combination with systemic steroids but strong evidence for this lacking. 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. The role of anti-fungal therapy is to reduce the antigenic load and accompanying immune response. The absorption of itraconazole is, however, poor and unpredictable. Consider oral voriconazole in cases where poor itraconazole absorption is suspected.

(Xolair®) a humanised monoclonal antibody directed against IgE has been used successfully in patients with refractory APBA and has a steroid sparing effect.

MONITORING TREATMENT

- 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 while on corticosteroids
- Ensure adequate calcium and vitamin D supplementation to minimise the risk of osteopaenia and osteoporosis

- Check for adrenal suppression if using steroids and anti-fungal combination regime
- Resolution of clinical symptoms together with spirometry and chest x-ray are mostly used in practise to determine response to treatment
- Serial IgE levels may be useful for monitoring treatment response but levels may not fall in all cases. Repeating serum IgE levels is recommended after 2 months of treatment and then again at 6 months or every 8 weeks for a year. Expect a drop of more than 35% in IgE level over 2 months of therapy as a positive response
- Remission is considered if no new symptoms occur after 6 months of discontinuing steroids and/or anti-fungals

PREVENTION

- Avoid damp, mouldy places (like stables, compost heaps)
- Check for moulds in the home
- Meticulous nebuliser hygiene

6.12 HAEMOPTYSIS

Minor haemoptysis and blood-streaked sputum is commonly seen in pulmonary exacerbations of CF. Atypical infections with non-tuberculous mycobacteria (NTMs) and vitamin K deficiency (particularly where there is CF liver disease) requires exclusion.

Major haemoptysis is defined as producing ≥240ml of blood within 24 hours, or recurrent bleeding of ≥100ml daily for several days. Approximately 4% of all patients with CF will suffer an episode of massive haemoptysis during their lifetime. Primary management of patients with CF and massive haemoptysis does not differ from haemoptysis seen in other forms of bronchiectasis. However, guidelines for the management of massive haemoptysis in patients with CF have been published, which make the following specific recommendations:

- NSAIDs should be discontinued because of their effect on platelet function
- All chest physiotherapy should be ceased during the period of active bleeding, as it may impair clot formation and adherence at the site of bleeding
- Aerosolised hypertonic saline should be ceased because of its propensity to cause airway irritation and cough
- There is debate about whether aerosolised antibiotics, inhaled DNAse and bronchodilators should be continued
- Unstable patients should be treated with bronchial artery embolisation (BAE). The role of BAE in patients with massive haemoptysis, which has stopped, is less clear: some studies have advocated that all large and suspicious bronchial arteries should be embolised to prevent recurrence; however, this is at the risk of potential complications of BAE such as spinal artery embolisation
- Lung resection for massive haemoptysis should only be performed as a last resort

6.13 SPONTANEOUS PNEUMOTHORAX

The incidence of secondary spontaneous pneumothorax (SSP) in people with CF is 0.64% per year. Approximately 1 in 25 people will experience a pneumothorax during their lifetime. This complication is more common in older patients and those with more severe airflow obstruction, and is recurrent in 50-90% of cases.

The treatment of SSP in patients with CF does not differ substantially from that in patients with other kinds of structural lung disease, although separate guidelines do exist. These guidelines are based on expert consensus opinion rather than high-quality data. They make the following recommendations specific to CF:

- Patients with a recurrent large pneumothorax should undergo pleurodesis, but pleurodesis is probably inappropriate after a first episode that has completely resolved. This differs from the management of SSP in other lung diseases, where surgery to prevent occurrence is usually performed during the same hospitalisation for the first episode, and prior to removal of the intercostal drain. This relates to the historical concern (generally overstated) that any pleurodesis procedure may influence a patient's suitability for future lung transplantation
    - Surgical pleurodesis is the preferred method; videoscopic-assisted thoracic surgery (VATS)-directed talc insufflation rather that VATS pleurectomy is preferred, as there is a greater risk for adhesions and bleeding complications during explantation of the native lungs, should transplantation be pursued
- Pneumothorax may be a manifestation of a pulmonary exacerbation, and consideration should be given to starting antibiotics if there is additional evidence of worsening infection and airflow obstruction
- Non-invasive ventilation (NIV) should be withheld from patients while the pneumothorax is present
- Spirometry should not be performed for 2 weeks after the pneumothorax has resolved
- Chest physiotherapy including maual percussion, positive expiratory pressure (PEP)/oscillating PEP devices should be withheld in patients with a large pneumothorax, although other airway clearance therapies can continue
- Inhaled therapies do not need to be discontinued in patients with pneumothorax

6.14 RESPIRATORY FAILURE, SUPPLEMENTAL OXYGEN THERAPY AND NONINVASIVE VENTILATION

As bronchiectasis and airway obstruction progress in CF, worsening ventilation-perfusion mismatching leads to hypoxaemia. This may initially occur only during sleep or exercise, and supplemental oxygen therapy may be required. Overnight oximetry should be performed to determine nocturnal oxygen requirements, and this should ideally be tested when clinically stable. The benefits of supplemental oxygen therapy are largely symptomatic, with modest improvements in exercise duration and capacity and improved work/school attendance. Supplemental oxygen may delay or ameliorate the complications of chronic hypoxia (such as the development of pulmonary hypertension and right ventricular failure).

Hypercapnia occurs relatively late in the course of CF lung disease. Ventilation is reduced during sleep, and this exacerbates hypercapnia; with symptoms of early morning headache and daytime fatigue often prominent. The use of supplemental oxygen can worsen hypercapnia by altering ventilation-perfusion relationships, but this increase is seldom clinically significant. Nocturnal non-invasive positive pressure ventilation (NIV) has been shown to improve symptoms, exercise capacity and nocturnal hypoventilation, and should be offered where

available to patients who remain hypercapnic despite optimisation of other therapies. NIV can also be used in hospital to treat acute respiratory failure during pulmonary exacerbations of CF, while waiting for other therapies like antibiotics, bronchodilators and physiotherapy to take effect. Any episode of respiratory failure should trigger discussions on quality of life considerations and end-of-life care or, where offered, referral for consideration for lung transplantation.

The need for endotracheal intubation and mechanical ventilation in patients with established chronic respiratory failure is associated with a very poor outcome, and should be avoided. In expert centres, veno-venous extracorporeal membrane support (VV-ECMO) or extracorporeal carbon dioxide removal (ECCO2-R) in awake patients with respiratory failure may be used as a bridge to lung transplantation.

6.15 LUNG TRANSPLANTATION IN CF

Transplantation remains the best option for prolonging life for many patients with CF with advanced lung disease. Although in South Africa lung transplant expertise and resources currently exist only at a single private sector centre, it is anticipated that this service will become more accessible in future. The number of lung transplants performed per year in SA is also limited by a significant shortage of donor organs.

Bilateral sequential lung transplantation is the only procedure recommended in CF lung transplantation. Single lung and living donor lobar transplants are not recommended.

Current international figures published by the ISHLT (International Society for Heart and Lung Transplantation), which includes data from the SA Netcare Milpark Hospital lung transplant unit, have presented estimated survival rates after lung transplantation overall and for CF (Table 6.5). Lung transplant in the setting of CF has a more favourable outcome compared to other conditions.

TABLE 6.5: SURVIVAL RATES POST LUNG TRANSPLANTATION – INTERNATIONAL FIGURES

Length of survival post BSLT	% chance of survival - all conditions	% chance of survival - CF patients
1 year	84.7%*	88.6%*
3 years	69.7%*	74.8%*
5 years	+-53%	+-62%
10 years	+-34%	+-45%

*ISHLT figures for BSLT performed between 1 October 2010 – 30 September 2014

Appropriate referral by a CF centre or treating pulmonologist to a lung transplant program, and then careful selection of appropriate recipients for listing by the lung transplant team, are important determinants of outcome.

In general, adult patients may be considered for lung transplant is they have:

1. >50% risk of death from transplantable lung disease within 2 years if lung transplantation is not performed.
2. >80% likelihood of surviving at least 90 days after lung transplantation.
3. >80% likelihood of 5-year post lung transplant survival from a general medical perspective, providing that there is adequate graft function.

The above guidelines are not CF specific. Projecting survival in patients with CF is difficult, however, the rate of decline in lung function has repeatedly been found to be a strong indicator of early mortality in CF. $PaCO_2$ >50mmHg, the need for nutritional supplementation, female gender, diabetes, *Burkholderia cepacia* infection and number of exacerbations have also been shown to be predictors of early mortality without transplant.

The decision to place a patient on the waiting list for a lung transplant is a complex process that takes into consideration individual clinical, psychosocial and program-specific factors and characteristics. The referral of patients to a transplant centre should not be interpreted by the patient, referring physician or the program as an automatic endorsement of listing. Referral **(**for consideration for transplantation) and listing are separate decisions.

Patients who do not currently qualify for transplantation, but may ultimately meet the criteria should not have referral delayed while undergoing corrective treatment.

CYSTIC FIBROSIS-SPECIFIC REFERRAL CRITERIA FOR LUNG TRANSPLANTATION EVALUATION

Early referral to the lung transplant program for assessment is essential and should occur early in patients who present with:

- FEV1 ≤30% of expected despite optimal medical therapy
- Advanced lung disease with
    - rapidly falling FEV1 despite optimal therapy, especially in a female patient
    - associated diabetes
    - 6-minute walk test <400m
- Development of pulmonary hypertension (Systolic PAP >35mmHg on ECHO or mean PAP >25mmHg measured by right heart catheterisation) in the absence of a hypoxic exacerbation
- Clinical decline characterised by an increasing frequency of exacerbations associated with any of the following:
    - An episode of acute respiratory failure requiring non-invasive or invasive ventilation
    - Increasing antibiotic resistance and poor clinical recovery from exacerbations
    - Worsening nutritional status despite supplementation
    - Pneumothorax
    - Life threatening haemoptysis despite bronchial artery embolisation
- Poor quality of life secondary to chronic respiratory failure despite optimal medical management
- The patient should actively and independently want transplantation

ABSOLUTE CONTRA-INDICATIONS TO LUNG TRANSPLANT IN CF

- HIV infection
- Active Hepatitis B and C infection

- Active *Mycobacterium tuberculosis infection*
- Active or chronic *Mycobacterium abscessus infection*
- Colonisation with *Burkholderia cenocepacia* (Genomovar III)
- Invasive aspergillosis
- Progressive or severe malnutrition despite optimal supplementation. BMI in CF patients should be a minimum of 18.5kg/m^2 but preferably above 20kg/m^2
- Extensive prior chest surgery e.g. lung or lobar resection. A history of chemical or surgical pleurodesis will be assessed by the transplant centre on an individual basis
- Invasive ventilation at the time of transplant
- A history of malignancy in the previous 5 years. There is a high-risk malignancy recurrence in the presence of immune suppression even after a 5-year disease free interval
- Untreatable significant dysfunction of other major organ systems
- Acute medical instability including but not limited to, acute sepsis, myocardial infarction and liver failure, at the time of transplant
- Significant chest wall or spinal deformity expected to cause restriction after transplant
- Non-adherence to medical therapy or a history of repeated or prolonged non-adherence to medical therapy
- Psychiatric or psychological conditions associated with the inability to co-operate with the medical/allied medical care team and/or adhere to complex medical therapy
- Absence of an adequate or reliable social support system
- Severely limited functional status with poor rehabilitation potential
- Substance abuse or dependence (e.g. alcohol, tobacco, marijuana or other illicit substances)

RELATIVE CONTRA-INDICATIONS TO LUNG TRANSPLANT IN CF

- ≥65 years of age
- Symptomatic osteoporosis
- SVC syndrome with limited large neck vessel venous access
- Colonisation or infection with highly resistant or highly virulent bacteria, fungi and certain strains of mycobacteria (e.g. chronic extra-pulmonary infection expected to worsen after transplantation)
- Severe/end-stage CF-related liver disease unless concurrent liver transplant is possible
- Chronic corticosteroid requirements > 20mg/day of prednisolone or prednisone

6.16 MULTI-ORGAN TRANSPLANTATION IN CYSTIC FIBROSIS

Candidates for combined lung-liver transplant should meet lung disease–specific criteria for lung transplant listing and have advanced liver disease as demonstrated by biopsy-proven cirrhosis and a portal gradient of >10mm Hg. Combined liver-lung transplant should not be considered in patients with albumin <18.0 g/dl, international normalised ratio >1.8, the presence of severe ascites or encephalopathy.

In some patients with less severe liver or lung disease, listing for a combined transplant may be appropriate if post-transplant organ dysfunction would be anticipated if the patient were to receive either single organ alone.

6.17 PHYSIOTHERAPY

AIRWAY CLEARANCE TECHNIQUES (ACT)

"Chest physiotherapy", incorporating a range of airway clearance techniques (ACTs), is an integral part of CF management. ACTs facilitate loosening, mobilisation and clearance of thick and tenacious sputum, in order to prevent airway obstruction, minimise respiratory complications, and maintain or improve pulmonary function and ventilation.

The choice of airway clearance method and device should be based on individual disease state, preference, compliance with therapy and the effectiveness and efficiency of the therapy. Choice of technique and application thereof must be constantly modified and adjusted according to individual circumstance, age and lifestyle changes throughout the lifespan of a person with CF.

Generally, ACTs should be performed twice daily in people with CF, and more often if there is a superadded infection. The exact frequency and duration of each session is variable and must be individually determined through consultation with a physiotherapist with expertise in CF management. There may be distinct benefits in terms of future compliance, if a regimen of bidaily physiotherapy is implemented early in life, even in pre-symptomatic infants.

ACTs should be taught to and administered by the caregiver in young children and in those unable to perform independent active techniques. Older children and adults with CF should be taught ACTs to perform independently. Regular visits to professional physiotherapists may assist in this process, but should not be relied on as the only source of airway clearance owing to:

i) inadequate frequency of treatment - very few people would be able to attend physiotherapy sessions twice a day, every day, which is the standard required for ACT in CF

ii) substantial financial cost

iii) dependence on a professional for airway clearance detracts from the ability of the person with CF and their family to manage their own lung disease and to recognise and react appropriately to a change in respiratory signs and symptoms, which might indicate pulmonary exacerbation.

INFANTS AND YOUNG CHILDREN

In infants and young children with CF, who are unable to perform independent ACT, caregivers should be taught how to perform passive ACT techniques as part of a home program of care. The most commonly taught ACTs are modified postural drainage, percussion, and vibrations or thoracic compressions ("conventional chest physiotherapy"). Other techniques such as infant positive expiratory pressure (PEP) therapy and assisted autogenic drainage (AAD), along with physical activity (e.g. bouncing on a ball) have emerged as feasible alternatives or adjuncts to conventional techniques.

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. Only the use of modified PD positions should be used (e.g. supine, semi-recumbent, alternate side-lying, prone horizontal and supported sitting) and the head-down PD position should be avoided. Physiotherapy should be performed before meals, or at least one hour after a meal, to minimise the risk of reflux, vomiting and aspiration.

From about one year of age, components of the active airway clearance techniques should be taught and encouraged, initially using playful blowing activities which encourage deep inspiration and often use purse-lipped breathing during active exhalation (hence PEP therapy, see below). Examples are blowing bubbles and toy windmills. The focus should be on achieving independence and autonomy in self-care by early adolescence and adulthood, and this is best achieved by teaching and encouraging active ACT and the components thereof from as young an age as possible.

Parents of infants or young children with CF should not be provided with a suction machine for home use, and children admitted to hospital with respiratory exacerbations should only be subjected to naso- or oropharyngeal suction if a spontaneous cough is not elicited during therapy and/or cough is not effective in clearing secretions in young infants and/or if a sputum specimen is needed. If parents are unable to effectively clear their child's secretions during their standard home-based ACT, and/or the child becomes very tired with treatment and/or shows signs of increased respiratory distress, then the child should be assessed with regard to the possible need for hospital admission.

OLDER CHILDREN AND ADULTS

CONVENTIONAL CHEST PHYSIOTHERAPY

Conventional chest physiotherapy (i.e. postural drainage and percussions/ vibrations/ thoracic compression) was previously the mainstay of airway clearance for people with CF. However, this approach is time consuming, requires a second person to administer the chest manipulations, and has been associated with significant complications, especially when combined with head-down PD positioning. Conventional chest physiotherapy is therefore generally only recommended for infants and young children, those unable to comply with active airway clearance therapy (e.g. advanced disease), or if there is a specific patient preference for this modality. Modified 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 matching. Head-down tilt is no longer advocated as other positions are as effective and less likely to cause GOR, hypoxia and dyspnoea.

ACTIVE CYCLE OF BREATHING TECHNIQUE (ACBT)

The active cycle of breathing techniques consists of cycles of breathing control (BC), thoracic expansion exercises (TEE), and the forced expiration technique (FET or huffing) (Fig. 6.4). ACBT 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 ACBT. ACBT can be performed by anyone who can follow instructions and is useful in all stages of CF disease. Furthermore, no equipment is required, making this an attractive ACT option for many people with CF. The FET/huff can be performed at different lung volumes, depending on the site of retained secretions – a low volume huff (small breath in and long huff out) clears the more peripheral airways whereas a high-volume huff clears the central airways.

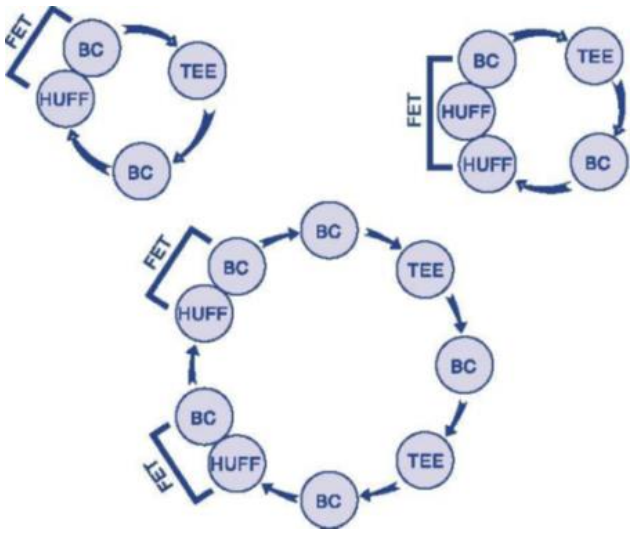

FIGURE 6.4: DIFFERENT WAYS OF PERFORMING ACBT

AUTOGENIC DRAINAGE (AD) AND ASSISTED AUTOGENIC DRAINAGE (AAD)

Autogenic drainage (AD) is a three-phase, independent breathing exercise that can be done in any body position. Breathing out actively (but not forcefully) from different lung volumes helps to "unstick, collect, and mobilise" pulmonary secretions. It is not a forced technique and may be particularly suitable for people who desaturate during conventional physiotherapy and/or in those with unstable or hyper-reactive airways, as airway closure is avoided. AD requires concentration and sensitivity to breathing levels and the location of mucus, and is therefore usually only taught formally to older children, adolescents and adults. However even very young children can be taught to "play" with different breathing levels and learn the feeling or sound of moving secretions.

Assisted autogenic drainage (AAD) uses the same three-phased approach of breathing at different lung volumes, however, the technique is passive with levels determined by external pressure on the rib cage. AAD is a useful alternative technique for infants and young children unable to perform independent AD, and in those who do not tolerate conventional physiotherapy. It may be performed on the therapist's/caregiver's lap, and can be combined with bouncing, ideally using a therapy ball.

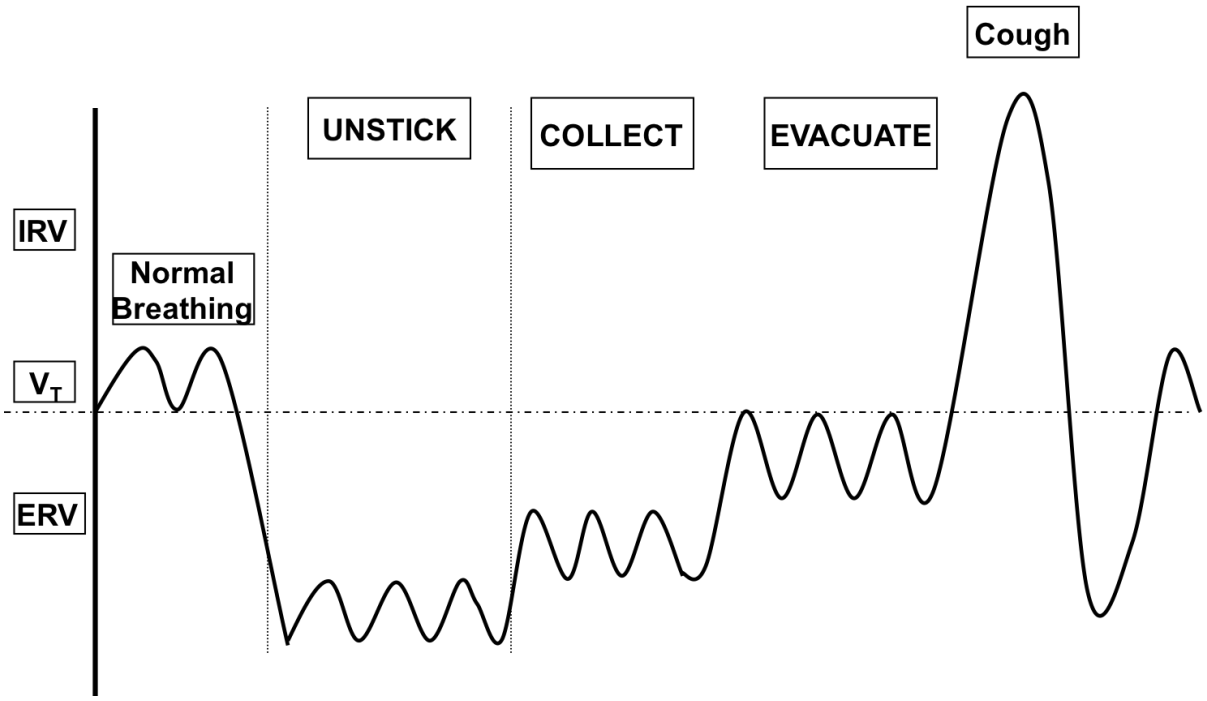

FIGURE 6.5: SCHEMATIC OF AD BREATHING VOLUMES AND LEVELS

POSITIVE EXPIRATORY PRESSURE (PEP) THERAPY

PEP therapy involves applying a resistance (usually between 10 and 20cmH_2O) to the expired breath (positive expiratory pressure). PEP therapy can be done using a PEP mask, PEP valve or a "blow bottle" - a bottle containing 10-20 cm of water into which a person blows through a wide-bore tube. PEP therapy may also be performed in younger children using different, fun apparatus through which the child blows through pursed lips (e.g. windmills, bubble blowing and musical instruments such as recorders and flutes).

PEP therapy helps to overcome dynamic airway collapse during exhalation, which is a particular problem in people with advanced CF airway disease and bronchomalacia, leading to air- and secretion trapping. Exhalation during PEP therapy is also used as an active force to mobilise secretions proximally (toward the mouth).

OSCILLATORY PEP THERAPY

Oscillatory devices apply oscillatory/vibratory resistance to expiratory airflow, which decreases the visco-elasticity of sputum and facilitates mucus clearance, while also preventing airway collapse. Frequencies between 8–16 Hz have been found useful for airway clearance.

Some of the common oscillatory PEP devices used in clinical practice include:

FLUTTER VALVE/LOCALLY MADE "BRONCH-U-VIBE®": A small plastic device containing a metal ball bearing, which repeatedly interrupts expiratory airflow, and produces a resistance of 10-25 cmH_2O and a range of airflow oscillation frequencies from 2–32 Hz, depending on the angle at which it is held.

ACAPELLA®: This uses a counterweighted plug and magnet to produce a resistance of 7-35 cm H2O and a range of airflow oscillation frequencies from 0–30 Hz.

CORNET®: A horn-shaped tube which houses a rubber inner tube. The inner tube uncurls as the individual blows through it.

- PEP and oscillatory PEP devices can be used independently or with minimal supervision, are highly portable, and there are inexpensive options available
- Oscillatory PEP therapy may not be effective in advanced CF disease with low airflow velocity and poor lung capacity
- Both PEP and oscillatory PEP are contra-indicated if there is frank haemoptysis and undrained 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
- Good infection control measures must be taken with all PEP and oscillatory PEP devices. Equipment should be thoroughly washed in warm soapy water after each use and be left to air dry completely before the next use. PEP "blow" bottles specifically must be emptied and both bottle and tubing thoroughly cleaned and dried after each use – water should never be left in the bottle between ACT sessions

HIGH FREQUENCY CHEST WALL OSCILLATION (HFCWO OR THE VEST)

An electric air compressor connects to an inflatable jacket (vest) and applies pneumatic vibration/oscillation to the entire external chest wall. Disadvantages to using HFCWO is that it is very expensive, fairly cumbersome, and is reliant on electricity. In addition, evidence suggests that HFCWO is less effective than conventional and other active techniques in both sputum clearance and maintaining lung function. HFCWO may be considered as an adjunct to regular active airway clearance therapy in specific cases, but should not replace active ACTs.

ORDER OF DELIVERY OF INHALED MEDICATIONS RELATIVE TO AIRWAY CLEARANCE:

The order of delivery of inhaled therapy relative to airway clearance is important and should be carefully explained to people with CF in order to optimise clinical effectiveness:

1. Short-acting bronchodilator (β2 agonist), if necessary, to prevent bronchospasm and open the airways to promote better secretion clearance.
2. Mucolytics (hypertonic saline/RhDNase): These should be given after short acting bronchodilators but usually before airway clearance.
    a. Dornase Alfa/rhDNAse/Pulmozyme® requires inhalation at least 30 minutes before airway clearance to ensure optimal mucolytic effect.

       Studies have suggested possible benefit of delivering rhDNAse after airway clearance, in order to break down uncleared sputum in more peripheral airways and/or to increase the dwell time for better clinical effectiveness, in preparation for the following ACT session. It is recommended that individuals be assessed regarding benefit or personal preference of receiving rhDNAse before or after airway clearance, always allowing more than 30 minutes before inhaling antibiotics.

    b. Hypertonic saline should be given immediately before chest physiotherapy.
3. Airway clearance (chest) physiotherapy, using any of the above- mentioned modalities

4. Inhaled antibiotics, corticosteroids and long-acting β2 agonists should be used after effective airway clearance in order to optimise deposition into the lungs.

EXERCISE

People with CF may be affected by decreased cardio-respiratory fitness, muscle strength, flexibility and endurance, and poor posture. Regular exercise, performed in addition to regular ACT, can slow the rate of pulmonary function decline, improve aerobic exercise capacity and improve quality of life.

In people with CF, exercise programmes should be:

- Individually tailored
- Frequently evaluated
- An integral part of the person's lifestyle

Physical training programmes must be enjoyable to optimise compliance, and should incorporate a range of types of exercise, including:

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

Aerobic exercise should ideally be 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 where possible. People with CF should not exercise to exhaustion, and measures such as the Borg Scale of perceived dyspnoea may be useful in gauging the optimal level of exercise.

SPECIAL CONSIDERATIONS

- If osteoporosis or osteopaenia is suspected or confirmed, care must be taken in prescribing weight training. Similarly, weight training should only be introduced after adolescence to minimise the risk of avulsion fractures in children before ossification is complete
- Modification of exercise type and intensity is necessary during acute infection, hypoxia, and following surgery
- In patients with CF-related diabetes, prolonged exercise may increase the risk of hypoglycaemia
- People with advanced CF lung disease may be at increased risk of exercise-induced hypoxia and may require supplementary oxygen during exertion if oxygen saturation falls to ≤90%
- Prolonged and/or intense exercise, particularly in hot climates such as SA, may increase the risk of dehydration and hyponatraemia or hypochloraemia in people with CF. Drinking isotonic sports

drinks (not containing excessive amounts of caffeine) rather than plain water may help to prevent some of these complications by replacing salt, fluid and energy. Because a person can lose between 0.5-1.5 litres of sweat per hour during exercise, and even more in hot weather; ideally people with CF should drink 500-600ml of fluid about two hours prior to exercise; 150 – 350ml immediately before activity and 150-200ml every 15-20 minutes during exercise

6.18 NEBULISERS, COMPRESSORS AND AEROSOLISED MEDICATION

Nebuliser therapy is commonly used in the care of people with CF to deliver inhaled medications, including antibiotics, mucolytics, and antifungals, for which pMDIs and DPIs may not be available. A nebuliser and compressor is issued to a specific person and is ONLY for that patient's use – respiratory equipment should never be shared owing to the danger of cross-infection.

NEBULISER TYPES

The amount of time required to deliver inhaled medications is important - the faster the drug delivery, the better the compliance with treatment will be. It is essential that the correct nebuliser is used to deliver CF-related drugs. Inappropriate use may 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 with different advantages and disadvantages related to CF (Table 6.6).

TABLE 6.6: NEBULISER TYPES

Nebuliser type	Description	Advantages	Disadvantages
Ultrasonic nebulisers	• Aerosol is created by vibrating the medication with a piezoelectric crystal at high frequency. • Aerosol is delivered continuously.	• Inexpensive • Fast delivery (reduced treatment times)	• Continuously release the drug throughout the respiratory cycle, so up to 70% of the drug is wasted during expiration. • Patients must have a regular breathing pattern • Can only be used for inhaled bronchodilators, normal and hypertonic saline. • ***** Ultrasonic nebulisation destroys (denatures) inhaled antibiotics and RhDNase*****
Jet nebulisers **Recommended for CF:** • **PARI TurboBoyS®** • **PARI Junior® Boy** • **PARI Sprint®** • **PARI Boy®** • **Phillips Respironics**	• An air compressor pushes air at high speed through a small opening into the nebulisation chamber (venturi system), thereby aerosolising	• Cheap • Robust • Able to produce fine droplets between 0.5 and 5 microns in size • Appropriate for all CF-related nebulised	• Relatively time consuming (10 – 15 minutes for 5ml of solution) • Does not stop automatically when the medication is

Porta-Neb® air compressor with Sidestream nebuliser®	the liquid medication. • Medication is delivered constantly though the respiratory cycle.	medications • Portable options are available which use car 12V sockets or batteries (e.g. Freeway Lite®; PARI Boy Mobile S®; PARI Trek®)	completed. • Medication is delivered throughout the respiratory cycle, thereby wasting some medication on exhalation. • Some jet nebulisers are not able to achieve sufficiently small particle sizes necessary for effective lung deposition. Nebuliser make and quality should always be checked before purchase and use.
Mesh Nebulisers Recommended for CF: PARI® eFlow Rapid (VMT)	• Use vibrating mesh technology (VMT), in which particles are aerosolised through a vibrating, perforated metal mesh. • Deliver the aerosol continuously throughout the breathing cycle.	• Small, homogenous particle sizes • Stops automatically when medication is finished. • Appropriate for nebulisation of all CF-related inhaled medications. • Silent. • Portable. • Efficient with very fast speed of delivery • Shorter treatment times result in less drug wastage than jet systems.	• Expensive • Break fairly easily
Adaptive Aerosol Delivery systems e.g. **Respironics® i-Neb**	• Use any of the above technologies, but also monitor breathing (by measuring pressure changes) and only delivers medication during inhalation.	• Quiet delivery of medication • Provides detailed monitoring including date, time, completeness of dose and time taken to nebulise. • Reduced drug wastage and improved delivery of medication as aerosol only delivered during inhalation.	• Expensive • Not readily available in SA • May require an alteration of the priming dose

NEBULISATION METHOD

A mouthpiece is the preferred route of delivery when using a nebuliser, as deposition into the lung is better. Therefore, young children using facemasks for nebulisation should switch to a mouth piece as soon as possible. People 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. It is better to hold the facemask slightly away from the face in a child who is not tolerating the treatment well rather than force it tightly on to the face and cause distress.

There are a number of different medications that might be prescribed for inhalation. If stored in the refrigerator, the medication should always be warmed to room temperature (not heated) before nebulising.

CLEANING AND MAINTENANCE OF NEBULISER EQUIPMENT.

The information sheet that accompanies the nebuliser device should always be read for instructions on cleaning and servicing.

1. Compressors:
    - Ideally, compressors should be serviced annually to optimise performance and check the electrics
    - The inlet filter should be changed every 3 months, or more often if obviously dirty
    - The compressor should not be kept on the floor as dust can be drawn in
    - The compressor should be wiped regularly with a clean, damp cloth to keep it dust-free
2. Jet nebulisers
    - Disposable nebulisers should be changed monthly, and should not be used for >3 months
    - Long-term (durable) nebulisers may last for up to a year
    - All nebuliser tubing, mouthpieces, masks, and reservoirs should be thoroughly cleaned after each use using warm soapy water, then rinsed in clear running water and dried with paper towel and then be allowed to air dry completely
    - Twice weekly the 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 steam sterilising 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 not recommended as a disinfectant as it does not adequately kill organisms such as S. aureus and E. coli***

3. Mesh nebulisers

- Must be washed after each use and sterilised one a week. Extra care must be taken as the mesh is easily damaged (the mesh should not be touched while cleaning)
- The mesh should be replaced every 6 months
- The Pari E-Flow Rapid system comes with an "easy-care cleaning aid", which backwashes the mesh, thus keeping the holes patent. This easy-care clean should be done once to twice a week, after normal cleaning and before sterilisation

6.19 INFECTION CONTROL CONSIDERATIONS

Infection control, both in the community and hospital (in- and outpatient) settings must be considered an integral component of the management of people with CF disease.

In the healthcare setting, organisms are generally acquired through one of three routes:

i) Direct or indirect contact with infected secretions.

ii) Droplet spread via large droplets from the respiratory tract that are usually suspended in the air for a short time.

iii) Airborne spread via small droplet nuclei that may remain airborne for prolonged periods of time, and may spread widely in a room or other enclosed space.

COMMUNITY PRECAUTIONS

- People with CF should try and separate themselves from anyone with an obvious respiratory tract infection
- Contact with warm wet environments (as might occur in hydrotherapy pools, spas or hot springs) should be avoided. Swimming pools are usually safe as long as they are adequately chlorinated
- People with CF should minimise exposure to moulds, which may be aerosolised during activities such as construction (building) and lawn mowing
- Activities involving animal excreta should be avoided where possible. Horse riding, for example, can be encouraged, but not cleaning out the stables. Similarly, household pets are generally acceptable as long as the person with CF is not required to clean out cages etc.
- A number of potentially harmful organisms occur in the soil and plant matter and therefore gardening is not an ideal recreational pursuit for someone with CF
- Home nebulisers are a potential source of infection. Nebulisers should be well maintained and components should be cleaned after use and sterilised regularly
- Respiratory devices such as spacers and airway clearance devices should be washed, disinfected and dried after each use.
- Family members should not share respiratory therapy equipment
- Unrelated children with CF may attend the same school. However, it is preferable, where possible, that these children be placed in different classes [*involvement in school activities is strongly encouraged*]

- Where possible, siblings with CF should have separate bedrooms. They should carry out their airway clearance and nebuliser treatments separately, using their own equipment

HOSPITAL PRECAUTIONS

- Standard infection control procedures must be adhered to at all times, including strict hand hygiene (washing with soap and water, or use of alcoholic hand disinfectant) after patient contact and environmental decontamination (e.g. cleaning equipment, surfaces, sinks etc.). Gloves should be worn for contact with body fluids and masks, gloves and goggles should be worn during procedures likely to generate splashes or sprays of body fluids or secretions

- Transmission-based precautions should be instituted according to microbiological findings:

- Contact precautions should be implemented where possible in cases of infection with multi-drug resistant organisms, MRSA, BCC and some respiratory viruses. This entails placing the patient in a private room, donning gloves and gown on entering the room, minimising transport of the patient out of the room, and dedicating non-critical equipment to that single patient

- Droplet precautions should be instituted in addition to standard precautions in the case of influenza and adenovirus infection. This entails placing the patient in a private room, wearing a high-filtration mask when working within one metre of the patient, and ensuring the patient wears a mask when leaving the room

- In addition to standard precautions, airborne transmission precautions should be implemented in the case of M. tuberculosis. Ideally, if people with proven pulmonary TB are admitted to hospital, they should be placed a room with negative filtration allowing six air exchanges per hour. Staff should wear high- filtration masks when entering the patient's room. Patient transport out of the room should be minimised and the patient must wear a mask if transport is essential

- People with CF should preferentially be admitted to a single, separate cubicle

- Contact between patients should be minimised by ensuring beds are more than one metre apart. Visits among in-patients should be discouraged, and family members should ensure that they also wash their hands thoroughly before and after contact

- Cough etiquette should be encouraged: instruct patients to turn away from others and cover their mouth and noses when coughing or sneezing; if a tissue is not available use the upper arm or sleeve, not the hand; discard tissues immediately into a covered receptacle or toilet; wash and dry hands or disinfect after coughing, sneezing or handling sputum and tissues; discourage handshakes and physical contact between people with CF; sit or stand a metre apart from other patients; do not leave sputum pots uncovered; and use disposable tissues rather than cloth handkerchiefs

- All people with CF should have their own oxygen, suction, nebulisation and airway clearance equipment. Equipment should not be shared among patients

- Nebulisation equipment should ideally be changed or sterilised every 24 hours. Sterile water is recommended as tap water may harbour a number of potentially pathogenic organisms

- Single- unit medication vials should be used where possible

- Any new CF inpatient facilities should consider providing negative pressure inpatient rooms, with adequate air exchange rates, to reduce the risk of airborne contamination

CLINIC PRECAUTIONS

- The benefits of attending a specialist clinic far outweigh any potential risk of infection. The greatest infection risk occurs in the community
- Cohort segregation based on sputum culture results is often not feasible or practical in the SA context, so attention to other infection control measures should be prioritised
- Regular sputum specimens should be obtained on all patients in order to monitor individual and prevalent pathogens, including potentially transmissible organism strains. Surveillance should ideally include genotyping, particularly all first- time *Pseudomonas* and *Burkholderia cepacia* spp. isolates
- Patients should ideally sit >2 metres apart on the waiting room benches to prevent direct transmission by droplet spread
- Patients should preferably not make physical contact or engage in close-contact play with other patients with CF
- Patients, staff and family members are encouraged to cover their nose and mouth when they cough or sneeze (and should wash their hands afterwards) – 'cough etiquette'
- After a patient has played with a toy or used any equipment in a clinic or waiting area, the item should be washed or decontaminated. Patients should be encouraged to bring their own toys, books etc. to clinic
- Waiting areas should be well ventilated and cleaned daily. Where possible, communal waiting rooms for people with CF should be avoided
- All clinic staff must adhere to standard infection control policies: hands must be washed and/or disinfected before and after patient contact, and all equipment used must be similarly disinfected between patients (e.g. stethoscopes, otoscopes etc.)
- Pulmonary function testing should be performed in a large well-ventilated space. Other patients should be kept more than two metres away from the person performing the test. Ideally, pulmonary function testing should be done in a negative-pressure room or in a room with high-efficiency particulate air filtration. Patients should disinfect their hands before holding the spirometer in order to prevent indirect transfer of organisms. Individual, disposable bacterial filters should be used for each patient performing lung function testing. Patients with drug-resistant or atypical organisms should perform lung function tests at the end of the clinic. The lung function equipment should be cleaned with disinfectant at the end of each clinic, or if it becomes soiled during use
- Collection of sputum specimens should be done in well ventilated areas, more than two metres from other patients. Ideally, this should be done in a negative-pressure room or in a room with high-efficiency particulate air filtration
- Sputum induction procedures should ideally be performed in a separate room dedicated for this function with negative-pressure ventilation and an acceptable number of air changes per hour
- Sputum containers must be sealed immediately after use and any soiled tissues etc. discarded
- Staff obtaining specimens should wear appropriate personal protective equipment

- Healthcare workers who are ill, particularly with respiratory tract infections, should either not attend clinic, where possible, or should wear surgical masks to minimise droplet spread of infected secretions

- All clinic staff and patients should be strongly encouraged to have seasonal influenza vaccinations

- Patients, families and hospital staff should receive appropriately targeted infection control education

CHAPTER 7. NUTRITION

Malnutrition is a common feature of CF, as result of high energy loss, higher energy needs, greater essential fatty acid turnover and decreased intake and absorption.

The secretion of digestive enzymes from the pancreas is severely reduced in most people with CF from an early age and, unless treated with pancreatic enzyme replacement therapy (PERT), the digestion and absorption of food are severely impaired. Symptoms of pancreatic insufficiency (PI) include malnutrition, poor growth and deficiencies of fat soluble vitamins A, D, E and K. Pancreatic sufficient (PS) patients may also have nutritional deficiencies.

Energy loss can be attributed to other metabolic changes associated with digestive abnormalities such as:

- Intestinal inflammation
- Small bowel bacterial overgrowth
- Low bicarbonate output
- Impaired insulin secretion leading to CF-related diabetes
- Impaired liver function

Malnutrition results in poor linear growth, and impaired respiratory muscle and immunological function. Malnutrition is strongly associated with reduced lung function leading to increased risk of morbidity and mortality. It is therefore essential that patients with CF be referred to a dietician experienced in the management of CF, and that nutritional status is comprehensively assessed at least once every quarter. Every effort must be made to achieve normal growth in CF as good nutrition promotes good quality of life and longevity.

The aims of nutritional management are to:

- Assess nutritional status
- Provide optimal energy and macronutrients
- Provide appropriate preventive nutrition counselling for caregivers of infants and children
- Provide nutritional support, including Oral Nutritional Support (ONS) and enteral nutrition (e.g. gastrostomy feeding)
- Prevent micronutrient deficiencies, particularly of fat soluble vitamins, iron and zinc
- Optimise PERT
- Provide appropriate sodium supplementation where needed
- Address psychosocial or behavioural factors influencing nutrition intake

7.1. ASSESSMENT OF NUTRITIONAL STATUS

Growth and nutritional status need to be assessed at a specialised CF clinic regularly. Anthropometric measurements should be accurately done and plotted against relevant growth charts. Growth pattern trends should be reviewed regularly.

GROWTH PARAMETERS

- Measurement of nutritional parameters should be taken frequently according to age, risk profile and nutritional status
- Infants and children under 5 require especially close nutritional monitoring
    - At every CF clinic visit, the child's weight and length/height needs to be measured as a minimum growth assessment requirement
    - Head circumference should be done for children under 3 years of age
- Body mass index (BMI) is a useful index, plotted on WHO charts for children over 5 years and standard tables for adults
- 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

NUTRITIONAL ASSESSMENT

Current growth chart standards used in SA are the WHO z-score charts of weight for age (WFA), length/height for age (HFA) and weight for length/height (WHZ). BMI charts are also available for children over 5 years of age.

TABLE 7.1. CLASSIFICATION OF MALNUTRITION

Age group	Classification of malnutrition
Infants and young children	• Expected weight-for-length/height: <85% • Weight-for-length/height Z score: - WHZ -2 to -3 [moderate] - WHZ < -3 [severe] • Growth faltering: weight loss or crossing centiles for 2-3 months
>5yr-adolescent	• Expected Weight-for-height: <85% • Weight-for-height Z score: - WHZ -2 & -3 [moderate] - Less than WHZ -3 [severe] • Growth faltering: weight loss or crossing centiles for 6 months • BMI Z score: - -2 to-3 [moderate)] - < -3 [severe]
Adults	• BMI <18.5 • Weight loss ≥5% over 2 months

An important part of nutritional assessment is to evaluate the dietary intake of patients with CF, in order to ensure that energy requirements are being met. Many people with CF have insufficient food intake. This can be multifactorial including anorexia (poor appetite), GOR, constipation, distal intestinal obstruction syndrome (DIOS) and psychogenic. A 24-hour recall should be done at every monthly visit for infants and at 3-4 monthly clinic visits for children, adolescents and adults. As part of their annual assessment, patients should record a 3-day food diary from which their nutritional intake is analysed and advised accordingly.

7.2. ENERGY AND MACRONUTRIENT REQUIREMENTS

Most individuals with CF have higher than normal energy requirements, due to poorly controlled intestinal malabsorption (PI, small bowel bacterial overgrowth, DIOS), increased energy expenditure, especially during pulmonary exacerbations, and in some cases increased energy loss (e.g. CF-related diabetes).

A diet that is high in both energy and protein is required to achieve normal weight gain and growth. Individual requirements vary but most people with CF need 120% to 150% more energy than people of the same age without CF. Certain individuals require up to 200% of energy requirements needed for the same age healthy population.

7.3. PREVENTIVE NUTRITIONAL INTERVENTIONS

INFANTS

Exclusive breastfeeding is recommended for infants with CF. Breastfed infants with CF have better lung function and fewer infections due to improved immune function and presence of docosahexaenoic acid (DHA). Most infants thrive well on exclusive breastfeeding, but if they demonstrate growth faltering then a breastmilk fortifier should be considered. Breastmilk has many advantages for infants with CF, including:

- Lipase and amylase content may partially compensate for reduced pancreatic secretion
- Immunological properties
- Optimal fatty acid profile for essential fatty acids

Standard infant formula is recommended if breastfeeding is not possible. Infants require between 150-180ml/kg/day of standard infant formula to meet their daily requirements. Standard infant formula can be provided with breastfeeding (approximately half total volume) should there be growth faltering. High energy dense infant formula can be considered should the infant demonstrate poor weight gain or if an infant struggles with maintaining the necessary volume of infant formula required a day.

Specialised infant formula, such as extensively hydrolysed or elemental formula, should only be considered for:

- Infants who have had gastrointestinal surgery, such as bowel resection with meconium ileus
- Infants with proven cow's milk protein allergy

Introduction of solid foods is recommended at the same age as for infants without CF, i.e. at 6 months of age.

FEEDING YOUNG CHILDREN AND ADOLESCENTS

The food intake of most patients does not meet their higher than normal energy requirements. Therefore, people with CF are encouraged to eat foods and snacks rich in energy such as oats, beans, sweet potatoes and

those rich in protein such as milk, cheese, biltong, eggs, nuts and chicken/meat/fish meat as part of their total balanced diet. Dietary sources of fat such as vegetable oils, peanut butter, butter and avocado can be added to food to maximise the energy density of a food serving. Sugary and unhealthy luxury items should be avoided, as in children without CF, as these may result in dental caries and poor eating habits.

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 eating foods with a high fat content is associated with abdominal pain or more frequent and paler stools, the dose of pancreatic enzymes should be increased whenever that food is taken. The dose should be gradually increased until the food is tolerated and steatorrhoea resolves.

It is very important that children are given frequent meals and snacks (5-6 per day) from a young age to maximise their 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.

7.4. NUTRITIONAL SUPPORT

Preventive counselling should be provided regardless of nutritional status. Diet should be assessed and adjusted individually, based on change in clinical needs and advice given on adequate calories, protein and micronutrients. The following criteria are a guide to different nutritional interventions required in individuals with CF (Table 7.2)

TABLE 7.2 CRITERIA FOR DIFFERENT NUTRITION INTERVENTIONS

Intervention	Less 5 years	Above 5 years	Adults >1 8years
Preventive counselling for NORMAL nutritional status	• Weight-for-length: 90%-100% • WHZ: >-1	• Weight-for-length: 90%-100% • WHZ: >-1 • BMI Z score: >-1	• BMI 18.5-22 (females) • BMI 18.5-23 (males) • No weight loss
Oral Nutritional Supplement (ONS)	• Weight-for-length: 85-89% • Weight loss or plateau over 4 – 6 months • WHZ: -2 & -3	• Weight-for-length: 85-89% • Weight loss or plateau over 6 months • WHZ: -2 & -3 • BMI Z-score: -2 &-3	• BMI <18.5 • Weight loss 5% last 2 months
Enteral nutrition via NGT or gastrostomy	• Implemented ONS and either • Weight-for-length:<85% • WHZ: ≤3 • Growth faltering 2 centiles	• Implemented ONS and either • Weight-for-length:<85% • WHZ: ≤3 • BMI Z-score: ≤3 • Growth faltering 2 centiles	Implemented ONS but persistent • BMI <18.5 • Weight loss 5% last 2 months

ORAL NUTRITIONAL SUPPLEMENTS (ONS)

If the patient's weight gain is inadequate or the appetite poor, oral nutritional supplements can improve energy intake (available products in SA listed in Appendix B). 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

ONS 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. PERT should be taken with ONS.

NASOGASTRIC AND GASTROSTOMY FEEDING

Supplemental tube feeds are frequently useful in patients with severe CF-related lung disease and poor nutritional status. Before embarking on these forms of feeding, diet must be optimised, PERT maximised and H2 blockers/protein pump inhibitors introduced. Introduction of tube feeding should be advised by a dietician experienced in CF management. Feeds are administered by either nasogastric or gastrostomy tube.

GUIDELINE FOR ENTERAL TUBE FEEDING:

1. Overnight feeding for 10-12 hours via enteral feeding pump (stop 2 hours before morning physiotherapy session).
2. Intermittent bolus feeding could be considered if a feeding pump is unavailable. The ideal volume could be administered in 2- 3 parts at different time periods, for example – at 9pm, 11pm and 6am.
3. Eat normally during the day. At least 40-50% of the total daily energy requirement should be given overnight.
4. Ideally use a peristaltic pump to avoid tube blockage.
5. An age appropriate standard polymeric tube feed product, ideally with medium chain triglycerides, should be provided. Specialised products such as extensively hydrolysed feed should only be given if there are proven on-going GI complications or previous GI surgery
6. The usual enzyme dose for a meal should be taken at the start of the feed and in the morning on wakening. An additional dose may be given before going to sleep. Enzyme capsules must be taken orally and NOT administered through the feeding tube as this may result in tube blockage and suboptimal enzyme bioavailability. In rare instances where children are unable swallow, guidelines to administer enzymes via a feeding tube are provided (see section 7.6)
7. Patients tolerate smaller volumes of higher concentration feeds (1.5-2.0 kcal/ml) better than larger volumes of less concentrated product.
8. Prokinetic agents may be considered, although few are available. Patients should be encouraged to sleep with the head of the bed elevated.

MONITORING FEED TOLERANCE:

- Vomiting, aspiration and increase in gastro-oesophageal reflux
- Hyperglycaemia in people with or at risk of impaired glucose tolerance or CF–related diabetes
- Leakage, bleeding or ulceration at the gastrostomy site

7.5. MICRONUTRIENT SUPPLEMENTATION

VITAMINS

All individuals with PI CF 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. Plasma fat soluble vitamin levels should be tested 3-6 months after initiation of PERT or if there is a change in therapy. Thereafter the plasma fat soluble vitamin levels should be checked annually and the dose adjusted accordingly.

VITAMIN A

Low levels of Vitamin A are associated with poorer clinical status, impaired lung function and increased pulmonary exacerbations. Vitamin A deficiency may cause night blindness in older patients. Clinical progress improves when low levels of vitamin A are corrected.

VITAMIN D

Vitamin D plays a role in calcium absorption and bone mineralisation. 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 with CF.

VITAMIN E

Vitamin E (alpha-tocopherol) serves as an antioxidant, protecting fatty acids from oxidative damage and preserving cellular membranes. Requirements increase in individuals with oxidative stress during pulmonary exacerbations of CF. Vitamin E deficiency may cause haemolytic anaemia in infants. In older individuals with CF, Vitamin E deficiency may cause neuromuscular degeneration, retinal and cognitive deficits.

VITAMIN K

Vitamin K plays role in blood clotting and bone health. Vitamin K levels may be low in people with CF, particularly if there is CF-related liver disease. Recommended supplementation of Vitamin K (0.3mg/kg/day up to 10mg daily) may be required if the INR is abnormal or if elective surgery is planned or if there is osteopaenia. Recommended dosages of fat soluble vitamins are presented in Appendix A

TABLE 7.3 NORMAL SERUM LEVELS AND MONITORING APPROACH FOR FAT SOLUBLE VITAMINS

Vitamin	Monitoring	Normal Serum values
Vitamin A	• Annual • Check 3-6 months after dose change	50-200mcg/dl
Vitamin D	• Annual • Check 3-6 months after dose change	Total 25(OH)D Deficient: <30nmol/L (12ng/ml) At risk: 30-50nmol/l(12-20ng/ml)
Vitamin E	• Annual • Check 3-6 months after dose change	Normal range: 3-18mcg/ml
Vitamin K	• 6-monthly in those with liver disease	Reflected by INR (abnormal > 1.2)

Examples of Fat soluble vitamin preparations available in SA include:

- 5ml standard “multivitamin” syrup contains 3 000U vitamin A and 400 IU Vitamin D3
- 0.6ml MVT drops (Kiddivit) contains 3 000IU vitamin A and 400IU vitamin D3
- Ergocalciferol (vitamin D) contains 5 000u/ml
- Calciferol 5 000 IU tablet can be given weekly and 50 000 IU every 2 weeks

- 1 alfa- Vitamin D available in 0.25 microgram and 1 microgram capsules. Only indicated in the presence of liver disease
- Vitamin E capsules 400 IU (approximately 10 drops, 3 drops=100U, can give 400U Monday/Wednesday/Friday))
- Vitamin K (injectable Kanakion) 2mg/0.2ml solution or 10mg un-scored tablets

MINERALS

IRON

Children with iron deficiency typically have poor lung function, poor appetite and overall poor health. Iron supplements are not routinely provided, but iron deficiency should be considered in the presence of anaemia. Full blood count should be monitored annually. Patients with moderate to severe lung disease require iron supplementation.

CALCIUM

Calcium plays a role in bone mineralisation together with Vitamin D. Therefore, those with vitamin D deficiency are also at risk of calcium deficiency. Calcium deficiency may be a result of poor intake and increased faecal calcium loss due to inadequate PERT. Calcium supplementation is recommended to maximise bone mineral accretion.

TABLE 7.4 RECOMMENDED DAILY INTAKE OF CALCIUM

Age	Dietary Reference Values
0-6 months	200mg
7-11months	280mg
1-3 years	450mg
4-10years	800mg
11-17years	1150mg
>18yr	1 000mg

Note: Titrilac (calcium carbonate) contains 168mg elemental calcium per tablet.

Calcium Sandoz contains 500mg elemental calcium per dispersible tablet

ZINC

Zinc deficiency has been associated with the following symptoms:

- Growth retardation
- Increased susceptibility to infections
- Delayed sexual maturation

- Eye problems
- Anorexia due to reduced sense of taste

If the child is malnourished at the time of diagnosis, zinc acetate should be given for a 6-month period:

- Infants 10mg daily
- Children >1yr 20mg a day

7.6. PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)

The majority of patients with CF (95%) are pancreatic insufficient (PI) and therefore require PERT. Enteric-coated microspheres are given to prevent inactivation of enzymes by gastric acid, thereby ensuring delivery of active enzymes to the duodenum.

High dose PERT preparations available in SA are listed in Table 7.5; and the recommended guidelines for PERT supplementation are presented in Table 7.6.

TABLE 7.5: HIGH DOSE PERT PREPARATIONS AVAILABLE IN SA

		Number of Units per Capsule		
	Age group	LIPASE	PROTEASE	AMYLASE
CREON®	Infants and young children	10 000	600	8 000
CREON 25000®	Older children and adults	25 000	1 000	18 000

TABLE 7.6: GENERAL GUIDELINES ON USE OF PANCREATIC ENZYME SUPPLEMENTS

<table>
<tr><td>Type</td><td>• Use one of the acid-resistant microsphere preparations.</td></tr>
<tr><td>Time</td><td>• 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 as the enzymes works best 25-30 minutes after taken.</td></tr>
<tr><td>Method</td><td>• 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 may be mixed with a little fluid and taken in one swallow.
• If mixed with breastmilk/formula or fruit puree, they should be mixed with one teaspoonful and taken in one or two swallows.
• Microspheres must not be chewed
• If child or patient is unable to swallow: microspheres should be dissolved in a 1:1 mixture of sodabic 8.4% and water, and allowed to stand for 10-15 minutes before administering through a feeding tube.</td></tr>
<tr><td>Dose</td><td>
<table>
<tr><td>Infants <1yr</td><td>• 2 000-4 000 U lipase/120ml formula or estimated breastmilk intake and approximately 2 000 U lipase/gram dietary fat in food</td></tr>
<tr><td>Children 1-4 years</td><td>• 2 000-4 000 U lipase/gram dietary fat, increasing dose as needed
• maximum dose 10 000U lipase/kg/day</td></tr>
<tr><td>Children >4yr-adults</td><td>Consider starting at 500U lipase/kg/meal, titrating to maximum dose of:
• 1 000-2 500 U lipase/kg/meal OR
• 10 000 U lipase/kg/day OR
• 2 000-4 000 U lipase/gram dietary fat taken with all fat-containing meals, snacks and drinks</td></tr>
</table>
• Enzymes are required with all meals and drinks that contain fat or protein.
• Start with ½ capsule (i.e. 3 000 to 5 000 units) in infants and one or two capsules per meal in older patients.
• Increase gradually until bowel symptoms are controlled.
• Increase the dose with more fatty meals.
• It is advisable not to exceed a dose of 3 000 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.</td></tr>
<tr><td>Additional</td><td>• Patients who require larger doses than recommended may warrant the addition of a proton pump inhibitor (PPI) to reduce gastric acid secretion.
• This may permit a reduction in the number of capsules required.</td></tr>
</table>

7.7. SODIUM SUPPLEMENTATION

People with CF have higher requirements for salt and other trace elements as a result of increased sweating, intestinal malabsorption and chronic inflammation. All infants with CF lose about 0.5 mmol/kg more sodium than non-CF infants. Infants are at further risk of sodium loss as breastmilk, formula and certain weaning foods are relatively low in sodium.

Additional risk factors for sodium loss are:

- Hot environmental conditions
- Fever
- Rapid breathing
- Fluid losses through stool and vomiting

Excess salt loss may cause clinical problems for people with CF, including poor growth in infants and young children. Hyponatraemic dehydration (with or without hypochloraemic metabolic alkalosis) may be a presenting feature of CF.

Routine salt supplementation is recommended in all infants < 1 year of age. In addition, salt supplementation should be considered in the presence of additional risk factors (Table 7.7). Salt intake should not be restricted but excessive salt intake is dangerous. Most SA diets contain sufficient salt to compensate for excessive salt loss.

TABLE 7.7: SODIUM SUPPLEMENTATION

Age	Sodium supplementation	Indication/method
Breastfed infants 0-6 months	1-2 mmol/kg/day	Salt in small portions diluted in water/fruit juice, or hypertonic saline solution (5%, 18%)
For infants with losses	Up to 4mmol/kg/day	Hot weather, fluid losses
Older children	Salty foods or sodium chloride capsules (1-3 per day)	Hot weather, fever, exercise/sports

Note: ¼ teaspoon salt = 25mmol or 575mg sodium

5% Hypertonic saline bottle = 0.9mmol/ml

18% NaCl Solution = 3mmol/ml

7.8. BEHAVIOURAL FACTORS RELATED TO NUTRITION INTAKE

Dietary counselling should be provided from early childhood through to adolescence and adulthood. Young children often show difficulty with new foods and may be fussy eaters. Parents should be provided with behavioural strategies with nutrition education, including:

- Encouraging family mealtimes for structure and routine
- If food is refused, do not offer an alternative

- Limiting mealtimes to 15 minutes for toddlers
- Having frequent, smaller meals through the day
- Positive reinforcement of good eating behaviours

Adolescents and young adults may demonstrate issues of body image, which should be closely monitored. Adequate intake should be encouraged together with a healthy lifestyle to support a positive body image during this period. Other psychosocial issues such as stress can also affect nutrition intake, particularly in young adolescents. Non-compliance in treatment is a common feature during adolescence, which contributes further to decreased nutritional intake.

CHAPTER 8. GASTROINTESTINAL PROBLEMS

8.1 GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)

GORD occurs commonly in individuals of all ages with CF. Typical symptoms are reported 6-8 times higher than in the general population, but more often disease is silent or considered as part of classical CF due to symptom overlap. GORD may have a significant negative impact on quality of life, nutrition and respiratory function.

Multiple factors contribute to the development of GORD, including:

- Increased gastro-oesophageal pressure gradient due to high negative intra-thoracic pressure with inspiration
- Increased intra-abdominal pressure due to frequent coughing
- Impaired intestinal motility and gastric emptying
- Increased gastric acidity
- Decreased basal tone of the lower oesophageal sphincter contributes to increased number, height, and time of reflux episodes
- High fat diet with post prandial fall in lower oesophageal sphincter tone and delayed gastric emptying
- Medication

Symptoms are unreported in most patients therefore a high index of awareness is essential, especially when there is:

- Unexplained progression of pulmonary disease despite optimal management and compliance
- Persistent vomiting
- Persistent abdominal pain
- Persistent failure to thrive

Given the possible late complications of GORD like Barret's oesophagus and malignancy, timeous treatment is important. The following is a recommended approach to suspected GORD:

1. Empiric trial of proton pump inhibitor (PPI) e.g. Esomeprazole 20-40mg (child 0.4-0.8mg/kg) od, omeprazole 20-40mg (child 0.4-0.8mg/kg) od
    a. The PPI should be taken in the morning on an empty stomach, 30 minutes before breakfast to ensure maximal efficiency
2. For rapid pain relief in severe cases initially add an H2-receptor blocker e.g. ranitidine 150mg bd (child 4mg/kg/dose every 6 hours) or cimetidine 200mg tds (child 5-10mg every 6 hours)
3. If no response after 4 weeks, investigate according to clinical presentation:
    a. Contrast radiography to exclude anatomical abnormality or stricture
    b. pH impedance or scintigraphy studies to confirm diagnosis

c. Endoscopy to evaluate complications or identify another cause for symptoms

4. Adjuvant therapy of a trial of pro- kinetic treatment may be considered

    a. Domperidone 10mg every 8 hours (child 0.4mg every 8 hours)

    b. Erythromycin 2mg/kg every 6 hours

    c. Metoclopramide 10mg (child 0.1-0.3mg/kg) every 8 hours

    d. Azithromycin

5. Surgical fundoplication may be effective in some patients

    a. In patients undergoing lung transplantation, surgery improved allograft function and reduced the incidence of bronchiolitis obliterans and chronic rejection

8.2 SMALL INTESTINAL BACTERIAL OVERGROWTH (SIBO)

SIBO, defined as a high bacterial count in the small intestine (>10^6 colony-forming units/ml intestinal fluid), occurs in 30-50% of people with CF. It results in synthesis of enterotoxic and unabsorbable metabolites that damage the mucosa, increase mucus production, deconjugate bile salts and disturb digestion and absorption. Symptoms include diarrhoea, nausea, abdominal pain, bloating and flatulence hours after meals. Steatorrhea despite adherence to PERT may also occur. Impaired digestion and absorption may further lead to anaemia, malnutrition and malabsorption.

Diagnosis relies on clinical suspicion, empirical treatment and assessment of response. Invasive culture of duodenal aspirates is not recommended and hydrogen breath test is considered inaccurate in CF due to elevated baseline levels from malabsorption. Treatment options include:

- Empirical antibiotics - metronidazole 400mg bd (child 7.5 mg/kg/dose every 8 hours) for 3 days
- Probiotics
- Prokinetics (erythromycin 2mg/kg every 6 hours) as adjunctive therapy in children
- In cases of associated diarrhoea, cholestyramine (e.g. Questran Lite) 1g every 6 hours for 5 days

8.3 INTUSSUSCEPTION

Intussusception in children with CF develops in 1%, with a peak incidence in infancy and again around 10 years of age. Thickened mucus, tenacious inspissated faecal matter adhered to mucosa or a chronically inflamed appendix, combined with a relatively hypotonic colon, contribute to more frequent intussusceptions. Asymptomatic intussusception may be common.

Typically, there is a sudden onset of abdominal colic, nausea and vomiting. Children present most often with acute bowel obstruction, while adults tend to present with a more chronic picture, with delayed diagnosis from 1 week to several months. Bloody stools may be present, and a mass may be felt in the right quadrant.

Ultrasound or MRI remains the diagnostic modality of choice (doughnut/bull's eye sign). Air and contrast enema may be used as a diagnostic as well as a therapeutic tool. Laparotomy and manual reduction may be necessary.

8.4 MECONIUM ILEUS

Meconium ileus (MI) is present in 15% of new-borns with CF. The incidence of MI is influenced by CFTR mutation type (class 1 and 2) as well as modifier genes (SLC6A14, SLC9A3, SLC26A9).

PRESENTATION:

- Most cases present with bilious vomiting, abdominal distention and failure to pass meconium within 3 days after birth. A right quadrant mass may be present
- MI can be simple or complex. In the simple type (50%), abnormal meconium obstructs the small bowel lumen at the level of the terminal ileum with proximal dilatation and a distally small encompassed bowel diameter. In the complex type (50%) the obstruction is accompanied by gastrointestinal pathology like peritonitis, volvulus, necrosis, perforation, pseudocyst formation or intestinal atresia. In one study 12% of patients with jejunoileal atresis had cystic fibrosis

DIAGNOSIS:

- Prenatal ultrasound shows hyperechogenic bowel, non-visualisation of the gallbladder, and dilated bowel
- Abdominal radiographs often show only dilated bowel without fluid levels. Sometimes there is a soap-bubble appearance due to mixed air and meconium. Calcified meconium may be seen
- A microcolon and meconium pellets in the terminal ileum may be seen on contrast radiographs

MANAGEMENT:

Due to the later risk of adhesions and DIOS, surgery should be avoided if possible. Evacuation of stools by N-acetylcysteine or gastrografin enemas combined with nasogastric decompression and correction of fluid and electrolyte balance is the recommended initial management strategy. Where surgery cannot be avoided, the obstruction can either be managed by a stoma with gut irrigation (excessive sodium losses may be a disadvantage) or by maintaining gut continuity with enterotomy, bowel washout, resection, if needed, and primary anastomosis. Recurrent obstruction and dysmotility may complicate the post-operative period. MI is not pathognomonic of CF, and appropriate tests should confirm the diagnosis in all cases.

MECONIUM PLUG SYNDROME

Meconium plug syndrome is a separate entity where abnormal meconium obstructs the colon rather than ileum. Mild abdominal distention may be present with failure to pass meconium at birth. A tight anal canal is present on rectal examination, but contrast enema shows normal colonic calibre with distal obstruction. Once the plug is expelled after rectal examination or enema, there is relief of symptoms. 25% of infants with meconium plug syndrome have CF.

8.5 DISTAL INTESTINAL OBSTRUCTION SYNDROME (DIOS)

DIOS is the accumulation of viscid faecal matter with the sticky bowel content adherent to the walls of the terminal ileum and caecum. The mass adheres strongly to the crypts and is not removed easily leading to complete or incomplete obstruction. Often DIOS is a permanent condition, with exacerbation of symptoms when

new material accumulates. It may present acutely with intestinal obstruction, or more often sub-acutely with abdominal pain and distension.

Typical findings include a palpable right lower quadrant mass, also visible on plain abdominal x-ray, accompanied by symptoms of abdominal pain, distension and vomiting.

- Risk factors for DIOS include:
- Severe CFTR genotype
- Pancreatic insufficiency
- Dehydration
- Poorly controlled fat malabsorption
- History of meconium ileus
- History of previous DIOS
- Post organ transplantation
- CF related diabetes
- Previous abdominal surgery

When DIOS is considered, it is important to exclude other common causes of abdominal pain in CF including:

- Constipation - symptoms are usually longstanding and faecal matter distributed evenly throughout the colon
- Appendicitis, appendicular abscess or mucocele of the appendix
- Intussusception
- Crohn's disease
- Adhesions
- Volvulus
- Fibrosing colonopathy
- Malignancy

Treatment reflects best practice with limited randomised controlled trials. In incomplete and moderate cases, it usually consists of

- Oral rehydration combined with an osmotic laxative containing polyethylene glycol (PEG). Iso-osmotic preparations include Klean-Prep, Golytely and Movicol. Doses of 2g/kg/day, maximum 80-100mg/day may be used or at 20ml/kg/h up to a maximum of 1l/h over 8 hours
- Gastrografin may be administered orally or per nasogastric tube: 50ml in 20ml juice for children < 6 years and 100ml diluted in 400ml on day 1, and half doses on subsequent days if needed

- N-acetylcysteine may be administered orally or per enema, but the efficacy is thought to be superseded by the above

Failure of treatment or persistent symptoms should prompt further investigation like abdominal sonar and CT to exclude other pathology.

In complete DIOS:

- Admission with IVI rehydration and nasogastric decompression is advised
- Gastrografin 100ml diluted 4 times with water can be used as an enema
- Local installation of Gastrografin in the caecum by colonoscopy has been described
- Surgery is seldom required and should be avoided if possible
- Non-opioid analgesia for pain

Prophylaxis after an initial episode includes maintenance laxative therapy, avoidance of dehydration and optimisation of pancreatic enzyme replacement.

Pre-transplant bowel preparation, postoperative bowel lavage and early enteral feeding with immediate introduction of pancreatic enzymes may prevent DIOS post lung transplant.

8.6 CONSTIPATION

Simple constipation is a frequent cause of abdominal pain and flatulence in the CF patient. It requires dietary management, sufficient fluid intake and enzyme replacement therapy as well as osmotic laxatives. Stimulant laxatives may be needed intermittently. Constipation should not be mistaken for fat malabsorption, and wrongly treated with increasing doses of pancreatic enzymes.

8.7 RECTAL PROLAPSE

Rectal prolapse occurs in approximately 3% of children with CF, and 3-11% of children with rectal prolapse have CF. In untreated patients, it may occur in up to 20% of cases. Rectal prolapse is common in toddlers with constipation, diarrhoea and malnutrition. In older patients, it can be triggered by cough. In most cases treatment of constipation, malnutrition and PERT resolves the prolapse, and surgery is rarely indicated.

8.8 COELIAC DISEASE

There is a strong association between CF and coeliac disease. Overlapping symptoms of impaired growth, muscle wasting, abnormal stools and abdominal distention may cause coeliac disease to be missed. It is advised that any person with CF >9 months of age, with persistent gastrointestinal symptoms, be screened for coeliac disease. Serologic screening includes a total IgA, transglutaminase-IgA (TGA), endomysium-IgA (EMA) and deaminated gliadin-IgA. Diagnosis should be confirmed by duodenal biopsies. Other causes for malabsorption such as lactose malabsorption, cow's milk protein allergy, enteric bacterial infections (giardiasis), small bowel intestinal bacterial overgrowth, pseudomembranous colitis, short bowel disease and Crohn's disease should be considered. Treatment consists of implementing a gluten-free diet.

8.9 APPENDICEAL DISEASE

The appendix can be affected in various ways, from mucus distention to acute inflammation, perforation and abscess formation, and clinical presentation may be atypical. Hypersecretion of the intestinal goblet cells is typical in CF and pain from a non-infected distended appendix is a distinct entity. The incidence of complications ranging from perforation, fistulisation and abscess formation is markedly increased when appendicitis occurs, and diagnosis is often delayed due to chronic abdominal pain, partial resolution of local inflammation by frequent antibiotic use and presumption of other diagnoses like DIOS. Ultrasound or CT scan may be used in the diagnosis, but due to the abnormal appearance of the appendix diagnosis may only be confirmed during diagnostic and curative laparotomy.

8.10 FIBROSING COLONOPATHY

Fibrosing colonopathy is a localised inflammation, fibrosis and thickening of the bowel wall, seen specifically in young patients with CF and associated with very high doses of PERT. To prevent this condition, pancreatic enzyme replacement should be limited to 2 500 units lipase per kilogram per meal or 10 000 units per kilogram per day.

8.11 INFLAMMATORY BOWEL DISEASE

Upregulation of genes associated with inflammation, PERT and gut dysbiosis all contribute to increased inflammation in the CF gastrointestinal tract. Although there are no specific associated symptoms, the contribution to growth failure should not be underestimated. Administration of probiotics like *Lactobacillus GG* and *L. reuteri* has been shown to decrease intestinal inflammation and abdominal discomfort. Emphasis on dietary unsaturated fat with anti-inflammatory ϖ -3 fatty acids is also advocated.

Overlap of signs and symptoms of Crohn's disease may delay diagnosis in the patient with CF. Severe weight loss, fistula formation, granulomata and perianal disease occurs frequently. The ileo-colic region is more often involved due to altered enterohepatic circulation. Increased incidence is age-related and the diagnosis should be considered in complicated cases.

8.12 GASTROINTESTINAL CANCER

Gastro-intestinal malignancy risk is increased in patients with CF, especially after transplantation. The most frequent malignancies include adenocarcinoma of the small intestine and colorectal cancer. Persistent inflammation, dysbiosis and high cell turnover is thought to play a role. With increased survival in CF, clear screening guidelines are needed, but not yet available. Risk factors appear to be increasing age, more severe CFTR genotype, transplantation and Caucasian ethnicity. Where symptoms are new, concerning or unresolved a high index of suspicion is necessary.

8.13 HEPATOBILIARY DISEASE

The liver is involved in most patients with CF, but clinically significant disease (multilobar cirrhosis with or without portal hypertension) is only seen in 5-10% of patients. Liver disease remains the third leading cause of death in CF and is responsible for 2.5% of overall mortality. A diagnostic approach is presented in Figure 8.1.

Liver involvement can be classified into 2 groups:

a) Advanced liver disease with cirrhosis and with or without portal hypertension, or

b) Other liver disease without cirrhosis or portal hypertension (manifesting as persistent or intermittent elevated liver enzymes (AST, ALT, GGT) > 2 times upper limit of normal, hepatic steatosis, hepatic fibrosis, cholangiopathy or other ultrasound abnormalities not consistent with cirrhosis).

The biliary tract is often involved and manifests as

- Cholangiopathy
- Cholestasis
- Gallbladder abnormalities (microgallbladder, cholelithiasis) and dysfunction

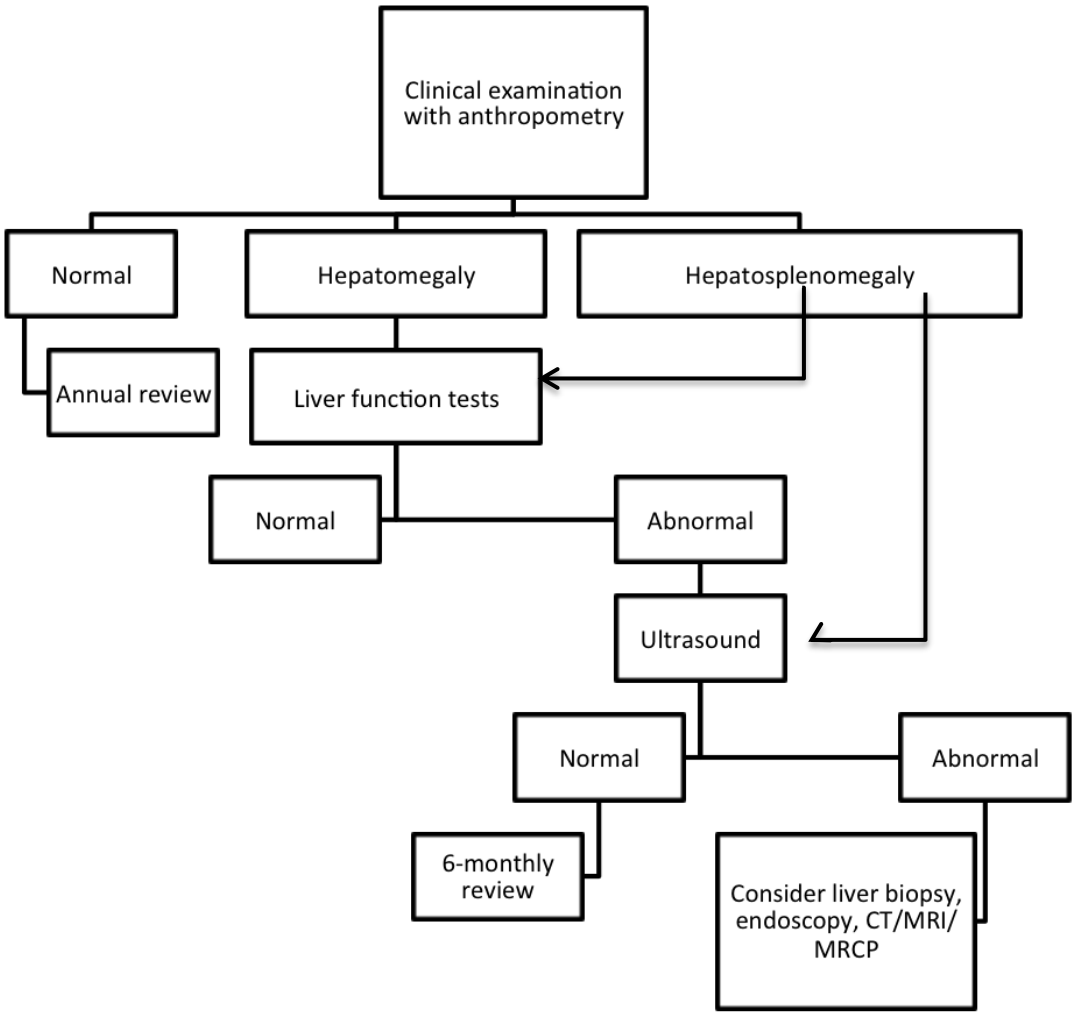

FIGURE 8.1: ALGORITHM FOR ROUTINE INVESTIGATIONS IN CF LIVER DISEASE.

MANAGEMENT

- Optimise nutritional status and lung health
- Supplement of fat soluble vitamins
- Ursodeoxycholic acid is the only available therapeutic modality that may prevent or delay progression of liver disease by:
    - Increasing bile flow
    - Replacement of toxigenic bile salts
    - Cytoprotective properties
    - Stimulating bicarbonate secretion in the biliary tract

Ursodeoxycholic acid at a dose of 15-20mg/kg/day in divided dosages has been associated with an improvement in AST, ALT, bile drainage, liver histology, nutritional and essential fatty acid status. It is internationally accepted as standard of care, despite the paucity of sufficient randomised controlled trials and need for further studies.

CF-RELATED CIRRHOSIS WITH PORTAL HYPERTENSION

Oesophageal and gastric varices have been reported in 30-100% of CF patients with cirrhosis, and complicated by bleeding in up to 28%. Management of acute variceal haemorrhage may include:

- Haemodynamic resuscitation
- Octreotide infusion 1-5ug/kg/h
- Band ligation of oesophageal varices
- Sclerotherapy of varices
- Broad spectrum empiric antibiotic therapy
- Antacid treatment with PPI e.g. Pantoprazole 20mg once daily IVI

Due to the risk of precipitating bronchoconstriction in the presence of pulmonary complications in CF, the use of non-selective beta-adrenoreceptor blockers as primary and secondary prophylaxis for variceal bleeding, is precluded. Transjugular intrahepatic portosystemic shunt (TIPS) is a treatment option in adult patients.

In patients with preserved liver function, surgical portosystemic shunting offers a more definitive treatment option. The presence of ascites usually indicates advanced disease with hepatic decompensation and a poor prognosis.

- Evaluation for liver transplant should be considered
- Diuretics furosemide and spironolactone can reduce the fluid load

8.14 INDICATIONS FOR REFERRAL FOR LIVER TRANSPLANTATION

The optimal timing for liver transplantation remain controversial and differs among centres – to transplant only once synthetic failure occurs, which rarely happens and is a late event, or when synthetic function is still

preserved but portal hypertension has developed. Established indications for liver transplant are the presence of liver cirrhosis with:

- Hepatic synthetic decompensation (albumin < 30g/L, increasing coagulopathy not corrected by Vitamin K)
- Development of jaundice and ascites
- Intractable variceal haemorrhage
- Severe malnutrition unresponsive to nutritional support measures
- Deteriorated quality of life due to liver disease

Outcomes are generally favourable and graft as well as one year survival is comparable with non- CF patients at approximately 90%, with beneficial effects on pulmonary function, nutritional status and quality of life.

Relative contraindications for isolated liver transplant include:

- Infections with multidrug resistant organisms (e.g. *Burkholderia, Pseudomonas*)
- Poor pre-transplant pulmonary function (FEV1 < 50% predicted)
- Elevated resting arterial pCO_2
- Extensive pulmonary fibrosis on imaging
- Severe pulmonary hypertension

CHAPTER 9. IMPAIRED GLUCOSE TOLERANCE AND CF-RELATED DIABETES MELLITUS

CF- related diabetes mellitus (CFRD) is associated with a nearly 6-fold increase in mortality. Early identification and treatment of CFRD has been shown to improve survival rates.

There are important differences between CFRD and both type I and type 2 diabetes, which necessitate a unique approach to diagnosis and management (Table 9. 1) and the involvement of an endocrinologist as part of the management team. Few people with CF have completely normal blood glucose levels at all times. The earliest change is variable, with intermittent post-prandial hyperglycaemia followed by impaired glucose tolerance (IGT), followed by diabetes without fasting hyperglycaemia, and ultimately diabetes with fasting hyperglycaemia. A diagnosis of ‘‘normal’’ glucose tolerance on oral glucose tolerance testing (OGTT) 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

9.1 PATHOPHYSIOLOGY

Abnormal chloride channels results in thick viscous secretions causing obstructive damage to the exocrine pancreas with progressive fibrosis and fatty infiltration. This results in disruption and destruction of Islet architecture, leading to loss of endocrine beta, alpha and pancreatic polypeptide cells.

- *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. 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 there may be loss of glucagon responses.
- *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.

TABLE 9.1. A COMPARISON OF TYPE 1 DIABETES, TYPE 2 DIABETES AND CFRD

	Type 1 Diabetes	Type 2 Diabetes	CF Related Diabetes
Clinical features			
Onset	Acute	Insidious	Insidious
Peak age of onset	Children & adolescents	Adults	18-24 years
Overweight	no	yes	no
Dyslipidaemia	no	yes	no
Ketosis prone	common	uncommon	uncommon
Microvascular Complications	Yes	Yes	Yes, but fewer
Macrovascular Complications	Yes	Yes	No
Pathophysiology			
Islets	Autoimmune destruction	Inherent β-cell defect	Exocrine tissue and islet destruction. Potential β-cell defect
Insulin status	Complete insulin deficiency	Insulin resistance Relative insulin deficiency	Partial insulin deficiency Episodes of insulin resistance
GLP-1	normal	Normal or decreased secretion; efficacy normal	Decreased secretion, improved with PERT.
GIP	normal	Normal or decreased secretion	Near-normal secretion; decreased efficacy
Treatment	Insulin	Diet, oral medication, insulin	Insulin

9.2 CLINICAL FEATURES:

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

9.3 DIAGNOSIS OF CFRD

- Oral glucose tolerance test (OGTT) is recommended
    - Annually from age 10 years

- Prior to transplant
- Prior to planned pregnancy
- During pregnancy

- Random and fasting glucose levels - while hyperglycaemia is diagnostic of diabetes, normal fasting or random glucose levels do not exclude a diagnosis of diabetes in CF
- Fasting and 2-hour post-prandial monitoring (PPG) is recommended
  - During hospitalisation
  - For outpatients during intercurrent illness, IV antibiotic use or systemic glucocorticoid use
  - Monthly if on continuous overnight enteral feeds
- Continuous glucose monitoring may aid the diagnosis of CFRD when considered in conjunction with the OGTT result and the clinical scenario
- HbA1c is unreliable in the diagnosis of CFRD. Importantly, while a normal HbA1c does not exclude CFRD, an HbA1c of *>6.5% is consistent with diabetes*

TABLE 9.2: CFRD DIAGNOSIS CRITERIA (ADAPTED FROM NORTH AMERICAN CF CONSENSUS COMMITTEE)

Test	Interpretation of OGTT mg/dL (mmol/L)			
OGTT		Fasting	2-h glucose	1-h glucose
	Normal	<126 (<7)	<140 (<7.8)	
	Impaired glucose tolerance	<126 (<7)	140 – 199 (7.8 – 11)	
	CFRD	≥126 (≥7)	≥200 (≥11.1)	
	Impaired glucose tolerance prior to pregnancy	<126 (<7)	<140 (<7.8)	≥200 (≥11.1)
	Gestational diabetes	≥ 92 (≥5.1)	≥153 (≥8.5)	≥180 (≥10)
Postprandial glucose monitoring (PPG)	CFRD	• Fasting glucose ≥ 126mg/dL (≥7 mmol/L) during hospitalisation • PPG ≥200 mg/dL (≥11.1 mmol/L) persisting >48 h during illness • PPG ≥200 mg/dL (≥11.1 mmol/L) during/after continuous night-time enteral feed		
HbA1c	CFRD	≥ 6.5% (<6.5 does not exclude CFRD)		
Random glucose	CFRD	≥ 200mg/dL (≥11.1 mmol/L) + polyuria & polydipsia		

9.4 MANAGEMENT OF CFRD

9.4.1 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 children and adolescents with CF and milder forms of abnormal glucose tolerance, although a small case series has demonstrated similar benefit. Choice of the insulin regimen depends on individual need and patient characteristics.

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.

TABLE 9.3 PRINCIPLES OF INSULIN THERAPY IN CFRD (TAKEN FROM MORAN ET AL: ISPAD CLINICAL PRACTICE CONSENSUS GUIDELINES 2014 COMPENDIUM MANAGEMENT OF CYSTIC FIBROSIS-RELATED DIABETES IN CHILDREN AND ADOLESCENTS. PEDIATRIC DIABETES 2014: 15(SUPPL. 20): 65–76)

General principles	• CFRD patients typically require 0.5–0.8 units insulin per kg body weight per day when they are in their usual state of health. Much more may be required during stress. • Because of the catabolic effects of insulin insufficiency, the goal is to give the patient as much insulin as can be safely tolerated. • Choose the insulin regimen that best fits the patient's lifestyle and meets the needs of their CF management.
Basal insulin	• Generally the goal is about 0.25 IU/kg body weight per 24 h; start at half this and adjust upward based on fasting glucose levels.
Meal coverage	• A common starting dose is 0.5–1 IU rapid-acting insulin for every 15 g of carbohydrate consumed. Insulin pens or syringes that deliver half units may be needed. • The dose is adjusted by increments of 0.5 IU per 15 g carbohydrate to achieve 2-h post-prandial blood glucose goals. • For very young patients or those who are unsure of what they will eat due to nausea or gastroparesis, the dose may need to be given right after the meal (although before is always better if possible). • Patients with CFRD without fasting hyperglycemia may be managed with pre-meal insulin alone, or with basal alone (depending on patient factors, including eating habits)
Correction dose (Sensitivity)	• Pre-meal correction is usually started at 0.5–1 IU rapid-acting insulin for every 2.8 mmol/L (50 mg/dL) above 8.3 mmol/L (150 mg/dL) and adjusted as needed.
Coverage of overnight drip feeding	• Frequently a single dose of regular/soluble plus NPH (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) insulin will cover an overnight drip feeding. The regular insulin covers the first half and the NPH the second half of the feeding. • Starting dose: calculate the total grams carbohydrate in the feeding, determine a total insulin dose based on the insulin to carbohydrate ratio (typically 0.5–1 units per 15 g), and deliver half of this as regular and half as NPH insulin. • Glucose levels 4 h into the feeding are used to adjust the regular insulin dose and those at the end of the feeding to adjust the NPH insulin dose. Occasionally a little rapid-acting insulin is also needed at the beginning. • Think of this as a 'long meal'. It does not replace basal insulin, and patients should only take this insulin when they have the feeding.
Limited care in a resource poor setting	• When analog insulin is not available, NPH insulin (e.g., Humulin N, Protaphane, Novolin N, Insulatard, Isophane, etc) and regular/soluble insulin can be used to treat CFRD, but care needs to be taken to avoid late post-prandial hypoglycemia. One possible regimen is NPH insulin at bedtime, and regular insulin with breakfast, lunch, and supper, in a patient who is eating three meals and three snacks a day.

TABLE 9.4 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 – may have restrict calories to prevent excessive weight gain	Usually require 120-150% (or more) of normal caloric intake for age and gender to maintain normal nutrition
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 (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 normal requirements
Salt	Low intake < 6g /day	Increased requirement - unrestricted intake

CHAPTER 10. OTHER CF- RELATED PROBLEMS

10.1 CF- RELATED BONE DISEASE (CFRBD)

CF- related bone disease (CFRBD) is manifested clinically with decreased bone density, pathological fractures and kyphosis. CFRBD is more likely in patients with malnutrition (low BMI, Vitamin D, K and calcium deficiency), severe lung disease, steroid therapy and physical inactivity. Late childhood and adolescence are critical periods when bone accrual during skeletal formative period is most rapid. It is essential that CFRBD is prevented and complications are recognised and managed promptly.

EARLY RECOGNITION OF REDUCED BONE DENSITY IN CF

Reduced bone density should ideally be measured using dual energy X-ray absorptiometry (DXA) in people from 16 years of age or as early as 8 years of age in those at risk:

- <90% ideal body weight
- FEV1<50% predicted
- Glucocorticosteroid use of ≥ 5mg/day for ≥ 90 days / year
- Delayed puberty
- A history of pathological fractures
- Post-transplant or are being assessed for transplantation

Thereafter DXA should be repeated in children and adults < 50 years of age:

- Every 5 years if the BMD Z-score is > -1
- Every 2 years if the BMD Z-score is between -1 and -2
- Every year if the Z-score is < -2 or if there has been a low trauma fracture

INTERPRETATION OF THE DXA SCAN IN CF

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 interpretation.

- The term "CF related low BMD" may be applied to children and adults with a BMD Z-score below -2. In children, adolescents or young adults with CF up to the age of 20 years, osteoporosis is defined as having a BMD Z-score < -2 and a significant fracture history
- In postmenopausal women and men over the age of 50 years with CF, osteoporosis is defined as having a BMD T/Z-score < -2.5
- In younger adults, osteoporosis is defined as having a BMD T/Z-score of < -2 and a significant fracture history

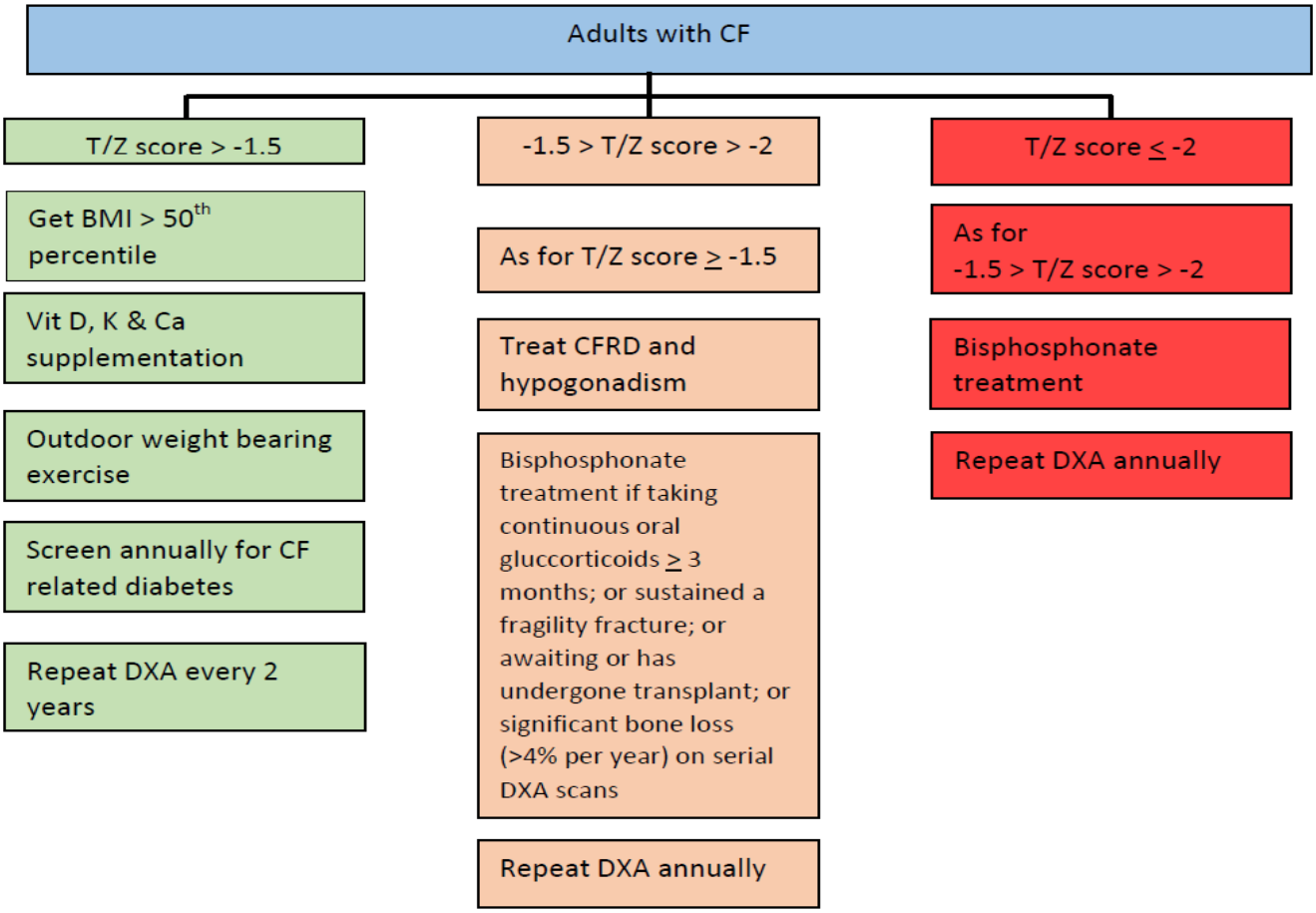

FIGURE 10.1 MANAGEMENT OF BONE MINERAL ABNORMALITIES IN ADULTS WITH CYSTIC FIBROSIS

NOTES ON TREATMENT:

For children, bisphosphonate therapy should be considered for:

- Taking continuous oral glucocorticoids ≥ 3 months with a history of low-trauma fracture, and/or BMD Z-score of ≤ -2
- BMD of ≤ -2 and awaiting or have received a transplant
- BMD of ≤ -2 and low-trauma fracture or vertebral compression fracture

All the usual cautions and contraindications for bisphosphonate use apply. In addition, it is important for patients to be well hydrated prior to receiving bisphosphonate infusions, and consideration should be given to pre-treating with paracetamol/ NSAIDs or glucocorticoid to prevent the severe bone pain that can occur after the bisphosphonate infusion.

10.2 BONE AND JOINT PAIN IN CF

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

CF ASSOCIATED ARTHRITIS (CFAA)

CFAA commonly presents with pain in the large joints including the knee, ankle, shoulder, elbow and wrist. The pain is episodic and usually lasts for less than a week. The arthritis is non-erosive, onset of pain is sudden and can often be disabling and there may be an associated fever and skin rash. CFAA may 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 10.2

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY (HPOA)

HPOA presents with symmetrical joint pain, usually involving the knees, ankles and wrists. Onset is more insidious than CFAA; pain is initially mild and the joint is swollen, tender and warm, often resembling cellulitis. X-ray of the involved joint may show periosteal elevation with new bone formation along long bones. Radio nucleotide bone scanning shows diffuse, intense and symmetrical uptake. HPOA is more common in patients with severe lung disease. Treatment – see Fig 10.2

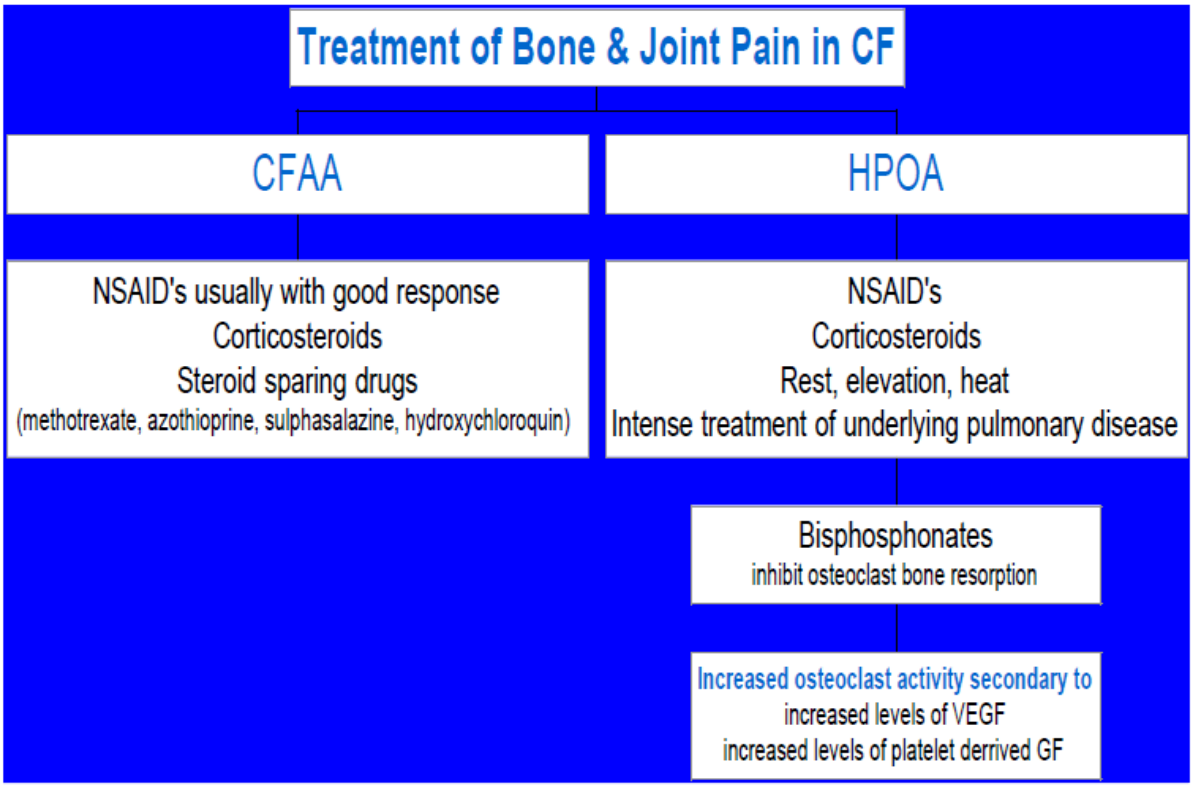

FIGURE 10.2 TREATMENT OF BONE AND JOINT PAIN IN CF

10.3 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 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 (50%). Prospective partners should therefore be screened for carrier status (see chapter 3).

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

Women with CF can use any available methods of contraception, but this should 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.

10.4 URINARY INCONTINENCE

Urinary incontinence 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 urinary incontinence, and this affects both airway clearance and daily life. It is important to ask the patient about incontinence as most people are too embarrassed to mention the problem. As the occurrence and severity of urinary incontinence increases with advanced CF disease, 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.

CHAPTER 11. PSYCHOSOCIAL CARE OF PEOPLE LIVING WITH CF

> *"There is no health without mental health"- CF Foundation, 2015.*

11.1 AT DIAGNOSIS

How patients and their families cope at the time of diagnosis largely determines how they will cope going forward. A diagnosis of CF affects every aspect of the life of the patient and their family, as well as those that support them. Families' needs at the time of diagnosis include:

- Understanding what CF is
- Developing a good relationship with the doctor and medical team
- Understanding the genetic implications of CF
- Meeting other families affected by CF

11.2 LEARNING TO LIVE WITH CF

Learning to live with CF is an ongoing and life-long effort. At different ages and stages of life, different coping strategies must be adopted. For example, the young child with CF needs his/her parents to be actively involved in all treatment, however an adolescent with CF should need less active involvement by the parents and more psycho-emotional support.

EARLY YEARS: Parents and caregivers need to be encouraged to provide a structured practice of physiotherapy, medical treatments and healthcare. The CF team can help the family by being supportive and providing clear information.

SCHOOL YEARS: Support to the child with CF can include informing teachers about CF, regularly speaking to the child about their experience of school and promoting a positive self-image for the child. It is important to keep an open dialogue between school teachers, the family and the medical team.

ADOLESCENT YEARS: during this transitional stage of life, issues related to identity challenge the young person with CF. The transition from a children's medical setting to an adult service may occur during this time. Decisions about future studies and career choices may bring about concerns of life expectancy and an existential crisis. During this time, a person living with CF needs to be reminded of their self-worth, the value of life and be helped to identify purpose and meaning in their life.

ADULT YEARS: Adults living with CF must learn to manage their work, family and health and requires ongoing psychosocial and psycho-emotional support. Therapeutic counselling and supportive listening can be of benefit, particularly at times of important life decisions.

END OF LIFE YEARS: Coping with death and dying is a challenge for most people. End of life should be discussed or explored before reaching this stage. Respite care in hospitals or hospice should be facilitated. Information is available from many sources and the most effective intervention is open communication, honesty and sensitivity among the medical team, the patient and family.

11.3 ORGAN TRANSPLANTATION

In consideration of the person with CF who is eligible for a transplant it is important to note:

- This procedure is done to promote life

- The side effects of an organ transplant may be debilitating
- Psychosocial maturity in the patient receiving the transplant must be evaluated properly before proceeding
- Sound understanding of the reasons for a transplant, risks, the procedure itself, demands and responsibilities of medical requirements post-transplant must be well understood by everyone in the family and the person living with CF
- How the person living with CF is prepared psychologically for transplant will determine future coping

11.4 COPING WITH CYSTIC FIBROSIS

FAMILY FUNCTIONING:

Families living with CF are affected by constant concerns around health, future and practical matters including financial responsibilities. Families are at risk of conflict and separation. Good family support is necessary for the health and well-being of the individual living with CF. The medical team will get to know the family during frequent consultations. Allowing the family to talk about their problems without fear or prejudice will facilitate better coping. Where family functioning is at risk, referral to a specialised family and/or parenting counselling service is advised.

ANXIETY AND DEPRESSION

People with CF and their families are at increased risk of depression and anxiety, which should be identified and treated appropriately. Psychological health plays an important role in physical health and symptoms of anxiety and depression affect both disease management and health outcomes.

Helping those affected by anxiety and depression begins by speaking openly about the person's individual experience and symptoms. Where necessary, patients should be referred to a counsellor or psychiatrist.

CYSTIC FIBROSIS AND IDENTITY

People living with CF need to establish their personal identity outside their diagnosis of CF. As social and psychological factors influence the development of personal identity, the person living with CF can be empowered to grow beyond their diagnosis of CF and establish a confident outlook and unique sense of self-worth. Simple questions about a person's preferences, lifestyle and ideas facilitate the development of personal identity.

The psychosocial challenges facing a person living with CF are varied and complex. Good intervention strategies designed to support the person over the long term are required. Table 11.1 highlights intervention and optimal outcomes for psychosocial and psycho-emotional support to the person living with CF.

TABLE 11.1 INTERVENTIONS AND OPTIMAL OUTCOMES OF PSYCHOSOCIAL AND EMOTIONAL SUPPORT

EVENT	INTERVENTION	AIM FOR SUCCESSFUL OUTCOME
Diagnosis	- Communication - Practical support, including facilitating state grant applications - Counselling and psycho-emotional support to family and other caregivers - Being available for questions as concerns arise - Include caregivers in designing coping strategies that will work	- Contain crises and facilitate acceptance - Aim for confident coping with CF in all areas of life - Deliver practical coping strategies
CLINIC APPOINTMENTS HOSPITAL ADMISSIONS MEDICAL PROCEDURES	- Ongoing psych-emotional supportive counselling - Encourage adherence and promote good health - Investigate problems interfering with coping, e.g. at home, and find workable solutions - Address fears and phobias, e.g. needle phobia, with appropriate psychological intervention - At times of major change in treatment, including organ transplant, be aware of risks and provide assessment and counselling. - Note loss of hope, future and loss of day to day functioning, respond and acknowledge appropriately	- Accept that most medical intervention can raise fears and phobias - Address fears and phobias with sensitivity - Aim to find workable solutions which fit the individual - Repeat these steps as new treatment becomes necessary.
DAY TO DAY STRUGGLES AND RESPONSIBILITIES	- Be available and supportive - Use ongoing psychosocial interventions, including: People Centred Approach, Cognitive Behavioural Therapy and Solutions Focussed Brief Therapy models - Keep regular contact, for example at clinic appointments. - Accept that requirements for coping will shift and change as the person living with CF grows and develops	- Show acceptance and willingness to support the person with CF over time
TALKING ABOUT DIFFICULT TOPICS	- Support medical team when difficult matters need to be addressed, including life expectancy, end of life issues - Provide open, supportive counselling to those who need to explore the difficult topic	- Reassure - Allow distress - Facilitate open communication - Encourage questions and discussion

	- Show compassion, sensitivity and be inclusive	- Contain the process until the difficult topic has been understood

CHAPTER 12. PALLIATIVE AND END-OF LIFE CARE IN CF

12.1 INTRODUCTION.

The World Health Organisation (WHO) defines **Palliative Care (PC)** as an approach that improves the quality of life (QOL) of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Although End of Life (EOL) care is an important part of palliative care, palliative care is not limited to the end of life. Ideally a palliative care approach should be started from the time of diagnosis and continue regardless of whether the patient receives treatment directed at modifying the underlying disease or not (Figure 12.1). The European Cystic Fibrosis Society Standards of Care: Best practice guidelines 2014 recommend that palliative care be integrated early in the care of the CF patient. This can be done by CF primary care providers in collaboration with specialist palliative care teams where necessary and available. Listing for lung transplantation should not be a barrier to palliative care especially considering the high morbidity and mortality in transplant candidates.

EOL care is the care of a person during the last part of their life, from the point at which it has become clear that the person is in a progressive state of decline. Terminal care is care provided in the last 48 hours when the patient is actively dying.

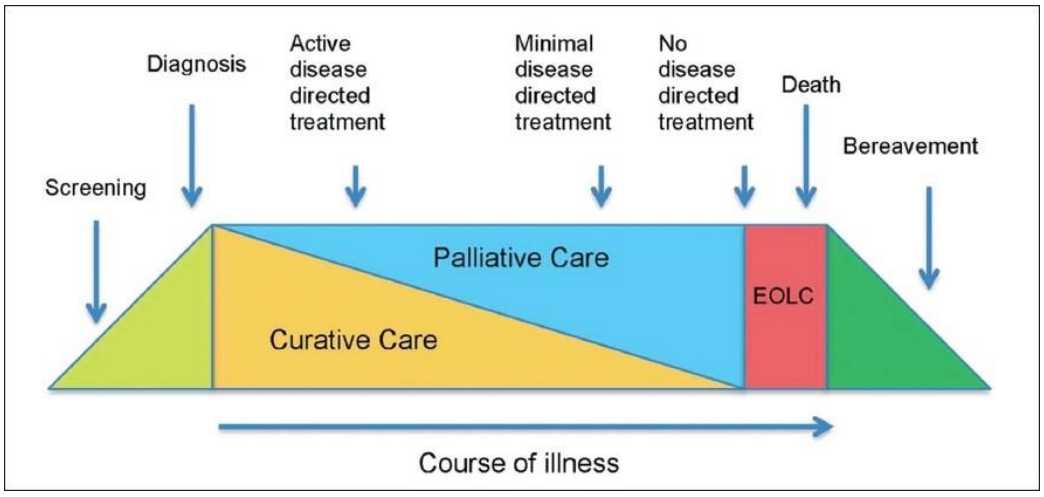

FIG 13.1: THE CONTINUUM OF PALLIATIVE CARE AND END-OF-LIFE CARE IN AN ILLNESS TRAJECTORY (MODIFIED FROM HTTP://DEPTS.WASHINGTON.EDU/PALLCARE/TRAINING/PPT.SHTML)

12.2 PALLIATIVE CARE FOR PATIENTS WITH CF

Palliative care helps patients and their families cope with the burden of a chronic illness through a team approach that addresses the patient's suffering in all domains and provides support to the family. Key palliative care competencies include the management of distressing symptoms, psychosocial care, advance care planning, terminal care and bereavement support.

12.3 SYMPTOMS AND TREATMENT

In many instances symptoms are resolved if the underlying cause is treatable or reversible, but with chronic illness this is not always the case. If the symptom is impacting negatively on quality of life then consideration should be given to the following:

1. Determine and treat the underlying cause of the symptom including non-physical causes, where appropriate
2. Use pharmacological and/or non-pharmacological measures
3. Treat symptoms without causing unacceptable side effects (consider drug interactions)
4. Determine whether the treatment is in the patient's best interests, weighing the burden of treatment with the potential benefit/harm.

12.3.1 PAIN SYNDROMES

Pain is a common symptom in patients with CF and should ideally be assessed at every clinical visit using standardised validated assessment tools. It increases with age and disease severity. The presence of pain is adults with CF are associated with lower quality-of-life scores, and increased incidence of depression and anxiety. Management of common pain syndromes is presented in Table 12.1.

Pain in CF may be caused by:

i. direct involvement of end-organ disease (e.g. abdominal cramping and pleuritic chest pain)

ii. physiologic changes related to end-organ disease (e.g. headaches from hypercarbia and sinusitis and musculoskeletal pain)

iii. Procedural pain (e.g. blood taking, inappropriate chest physiotherapy)

TABLE 12.1. MANAGEMENT COMMON PAIN SYNDROMES IN CF.

Site	HEADACHE AND NECK PAIN	CHEST PAIN	BACK PAIN	LIMB/JOINT PAIN	ABDOMINAL/PELVIC PAIN
Incidence	33%	10 - 37%	6%	17%	42 - 50%
Causes	Hypercarbia/hypoxia Sinusitis Muscle tension Migraine	Mostly musculoskeletal Pleural: pleuritis, effusion, pneumothorax Rib fractures (severe cough)	Mostly musculoskeletal Referred visceral pain (Pleural effusion, renal stones) Compression vertebral fractures and osteoporosis	Musculoskeletal CF associated arthritis Pulmonary hypertrophic osteoarthropathy, antibiotic side effects.	Peptic ulcer disease, gastritis, GORD, pancreatitis, biliary disease, kidney stones, DIOS, constipation, gynaecological
Disease directed therapies	Consider non-invasive ventilation Manage Sinusitis Avoid known triggers for migraine	Treat reversible underlying causes as above	Treat reversible underlying causes as above Refer orthopaedics if needed Evaluate bone mineral density and improve calcium/Vit D status	Pathology poorly understood Occasionally associated RA – refer rheumatology Consider hydroxychloroquine and gold salts	Treat reversible underlying causes as above Antacids: PPI's. DIOS: may require IV fluids, NGT and enemas
Non-drug management	Rest, warm drink Lie down in a dark room Massage or Transcutaneous electrical nerve stimulation (TENS) for tension headaches	Positioning TENS Strapping	Physiotherapy & exercise Posture correction TENS Back brace (fractures) Surgery only if indicated	Physiotherapy Bracing (temporary) Local measures: Hot/cold packs	Rehydration Dietary modifications Abdominal massage Surgical intervention as indicated

Drug-management	Paracetamol and/or NSAID (Ibuprofen) Unless contra-indicated **Migraines** **Acute:** Oral or nasal Sumatriptan (>12 years) with NSAID or paracetamol Anti-emetic (Metoclopramide) **Chronic:** Consider Propranolol prophylaxis if severe (avoid Tricyclic antidepressants-associated with thickened secretions)	**Step 1:** paracetamol +/- NSAID: high dose Ibuprofen associated with better lung fX (unless contra-indicated e.g. renal disease, GIT bleed) **Step 2**: Weak opioids: Tilidine (Valoron) or Tramadol > 12 years. NO CODEINE. **Step 3**: Strong opioids (do not combine weak and strong opioid): Morphine: start with lower dose 0.2- 0.4mg/kg with adjustments for renal impairment (increase 6hrly as needed). Consider use of transdermal fentanyl patches NB: Prevent & manage opioid related side effects **Consider adding co-analgesic (adjuvant)** especially if associated neuropathic component: Gabapentin or pregabalin		Usually responds to NSAIDs. Consider Selective Cox 2 inhibitors for long term use	Avoid NSAIDs if risk of upper GIT bleeding. Manage associated nausea and vomiting with anti-emetics Opioids may be required for severe pancreatitis and renal colic
Other		**Thoracic epidural** used successfully in patients with severe pain where opioids not tolerated	**Bisphosphonates** may be considered		

12.4 PALLIATIVE CARE PLANNING

Holistic care planning incorporating a bio-psychosocial model should occur early in the course of the illness through a MDT based approach. In the early stages, this consists of:

- Breaking the news of the diagnosis once confirmed and assisting with containment
- Ensuring insight and understanding of CF by the parent/family and development of coping strategies
- Disclosure and age-appropriate explanation to the child/patient.
- Honest conversations about severity, prognosis and life –limitations that still maintain hope
- Treatment adherence counselling
- Crisis management plans for intercurrent complications
- Assistance with mitigating impact on family through the involvement of community based resources where available
- Communication with schools/places of work
- Transitioning to adult services
- Psychological support and social assistance where needed.
- Sibling understanding and support
- Addressing spiritual concerns (why me/us?)

During end of life stage, the following are important:

- Talking about disease progression and management options/limitations even in patients listed for transplant
- Open honest conversations (age-appropriate) about death and dying
- Setting of goals
- Advanced care planning (children) and directives (adults)
- Terminal care planning including preferred place of care
- Anticipatory grief work with patient and family: preparing siblings, memory work, legacies and wills
- Funeral planning
- Bereavement care

ADVANCED CARE PLANNING (ACP) IN CF

The European CF Society Standards of Care: Best Practice Guidelines (2014) recommend early discussions to "allow time to psychologically adjust and carefully consider options at the end of life". Although ACP can be done at any time it is most commonly begun when the child/adult enters a state of progressive decline and returns to a lower baseline after an exacerbation. Although prediction of short-term mortality is difficult, there are models that may provide guidance, many of which were developed to stratify suitable lung transplant candidates.

Useful end-of-life clinical indicators include:

- Inability to maintain metabolic compensation for chronic respiratory acidosis,
- Presence of pulmonary hypertension
- Accelerated rate of decline in pulmonary function despite aggressive therapy
- Lack of response to prolonged IV antibiotic therapy
- Increasing frequency of exacerbations requiring antibiotics/ ICU admissions
- Refractory and/or recurrent pneumothorax
- Recurrent haemoptysis
- Weight loss that cannot be halted or reversed by supplemental feeding or TPN
- FEV1 < 30% or rapid decline in FEV1 (especially in females)
- Increased oxygen need, hypercapnia and need for NIV.
- Patients who are not eligible for transplant

ACP is the process of discussions culminating in a document, and not a document in itself. It is only a guideline and needs to be regularly revised and updated as circumstances change. Advance care directives are only legal documents for adults. ACP should include discussions with relevant healthcare professionals, the parents/caregiver and the patient him/herself where appropriate. The right of the adult or child patient to participate in decision making processes and to receive sufficient information about their disease and care should be respected. Even patients listed for transplantation should consider developing ACPs.

12.5 PALLIATIVE CARE EMERGENCIES IN CYSTIC FIBROSIS:

The most common and frightening palliative care emergencies that are also potential end of life events in cystic fibrosis are pneumothoraxes, haemoptysis and respiratory failure.

PNEUMOTHORAX

The causes, risk factors, clinical presentation, management and prevention of recurrence are covered in Chapter 6. From a palliative care perspective, considerations in the management of pneumothorax in cystic fibrosis include the need for emergency management of severe sudden onset dyspnoea and often associated anxiety (Table 12.2).

TABLE 12.2: EMERGENCY MANAGEMENT OF SUDDEN ONSET DYSPNOEA/ANXIETY, INCLUDING THE USE OF BUCCAL AND RECTAL ROUTES IN THE ABSENCE OF IV ACCESS (FROM ASSOCIATION FOR PAEDIATRIC PALLIATIVE MEDICINE (2017)).

Indication: • Agitation/ Anxiety/ Dyspnoea	Buccal dose	Oral or Gastrostomy dose	SC or IV stat dose	SC or IV infusion dose over 24 hours
neonate	25 micrograms/kg	50 micrograms/kg	25micrograms/kg Repeat at hourly intervals as needed	0.5-1 mg
1 – 2 months				
3months – 11 months				0.5 – 2 mg
I year – 5 years	50 micrograms/kg	100micrograms/kg		1- 2.5 mg
6 years -10 years	100 micrograms/kg Max single dose 5 mg			2.5 – 5 mg
11 years to 18 years				5-10 mg
	Maximum initial dose if 6-10yrs benzodiazepine naïve = 2.5mg. Can repeat after 10 minutes if required. Titrated according to response	Max single dose if benzodiazepine naïve = 5 mg		The above are guideline starting doses. Increment by 25-50% as needed.

Note:

- Buccal (Buccolam oromucosal solution) midazolam is not licensed for use in infants less than 3 months of age.
- Recommended SC/IV doses vary enormously in the literature. If in doubt, start at the lowest recommended dose and titrate rapidly.
- Onset of action by buccal and intranasal route 5-15 minutes. Time to peak concentration 30 mins. Half-life 2-5 hours. For buccal administration, if possible, divide the dose so half is given into one cheek and the remaining half into the other cheek.
- Onset of action by oral or gastrostomy route 10-30 minutes.
- Onset of action by IV route 2-3 minutes; SC route 5-10 minutes.
- Both high and low doses can lead to paradoxical agitation.
- Caution in known hypersensitivity; renal failure; hepatic or cardiac impairment; neuromuscular respiratory weakness; pulmonary insufficiency.

PAIN CONTROL WITH INSERTION AND WITH REMOVAL OF AN INTERCOSTAL DRAIN

Where possible good procedural pain management including local anaesthetic infiltration prior to the insertion of an intercostal drain should be practiced minimising pain and suffering related to management of this life-

threatening complication. The removal of intercostal drains is also associated with significant pain and is often undermanaged.

Patients with pneumothoraxes often have significant underlying lung disease which may require ongoing management of dyspnoea and/or chest pain. Low dose opioids (morphine) can be safely used even if patients are not ventilated provided attention is paid to titration against symptoms and adjustments made for renal dysfunction if present (Increase dosing interval to 6-8 hourly). Doses of 30 - 50% of pain doses are sufficient to manage dyspnoea. If available Fentanyl is the opioid of choice in patients with significant renal dysfunction. Where pain is present, pain itself is the physiological antagonist to the respiratory depressant effect of opioids. Caution should be exercised when combining opioids with benzodiazepines in patients with respiratory compromise. The doctrine of double intent may be relevant in patients at the end of life where adequate control of discomfort is an important goal.

The experience of a life-threatening event such as a sudden pneumothorax is extremely distressing for patient and family alike. Apart from physical discomfort and anxiety an event of such a nature can also provoke existential spiritual crises and questions about death and dying if these have not already arisen. It is an important trigger to increase the provision /focus on integrated palliative care provided by the primary team or prompt referral to a specialist palliative care service if needed and available.

HAEMOPTYSIS (OR OTHER LIFE-THREATENING BLEED)

Haemoptysis is a common complication in patients with CF and may range in severity from scant to massive. Massive haemoptysis is defined as >240ml/day or > 100ml/day for several days (see chapter 6). The prevention of recurrence in survivors depends on access to interventional radiology (e.g. bronchial artery embolisation) and/or thoracic surgery and operative risk of patients which is usually considerable as it most commonly occurs in patients with advanced illness.

The chances of massive haemoptysis being a terminal or pre-terminal event are high. As with patients with sudden onset pneumothorax, this is a frightening and traumatic event both for the patient and family. In the event of a sudden massive bleed, patients may lose consciousness from exsanguination and ensuing hypovolaemic shock.

In case where consciousness is preserved, anxiety high and death inevitable consideration should be given to the use of rapid sedation. The use of dark towels and sheets can be invaluable in this situation as the sight of large amounts of red blood against white sheets can intensify distress.

12.6 RESPIRATORY FAILURE

The natural history of CF lung disease is progression to advanced airway obstruction and eventual respiratory failure. The management of respiratory failure depends on available resources and patient preferences. ACP is essential in patients with respiratory failure and should ideally be done long before this point is reached.

SUPPLEMENTAL (HOME) OXYGEN AND NIV:

Decisions regarding the provision of supplemental oxygen and NIV support if available need to be individualised and based on an evaluation of risk vs benefit in the patient with advanced disease.

TABLE 12.3: POTENTIAL RISKS AND BENEFITS OF SUPPLEMENTAL OXYGEN AND NIV

Potential Benefits	Potential Risks
• Good palliation of dyspnoea (could also be achieved with low dose morphine) • Improved quality of life and sleep • Improved work of breathing-decreased catabolism, improved weight	• Psychological dependence on oxygen • Social isolation (esp. if transport cylinders not available) • Local complications (skin, pressure sores) • Prolongation of poor quality life • Difficulty withdrawing • Increased likelihood of developing more traumatic end of life complications: e.g. pneumothorax and haemoptysis

INVASIVE VENTILATION AND ICU CARE.

The role of invasive ventilation for patients with end-stage pulmonary disease is controversial and associated with poor outcomes. Ventilation could be considered for patients who develop respiratory failure with an acute reversible complication where recovery is anticipated (haemoptysis, pneumothorax, influenza, post-operative). Although there is no legal or moral distinction made between withholding or withdrawing invasive ventilator support, withdrawing support is often a more difficult decision for all concerned.

12.7 TERMINAL CARE

The terminal phase of an illness is defined as the last 48 hours of life. Owing to difficulties in prognostication as well as sudden end-of-life events this period may be difficult to anticipate. The terminal phase usually starts when the patient who is already in his/her end of life phase (which can last months to years in CF) appears to be actively dying or when a decision is made to withdraw or withhold life prolonging therapies in a patient who was already deteriorating.

Common practices and principles in terminal care for consideration in CF:

1. Shift in focus from prolonging life to achieving a good death, with comfort as the main driver of decision making. Inform family and patient (where appropriate) of the change in condition.

2. Maximise opportunities for communication between patient, caregivers and family. Relax visiting restrictions in hospitals but also be aware of emotional drain on patient and family. Identify family member to be liaison person/spokesperson for the family.

3. Feeding in terminal care is for comfort only and not to meet nutritional requirements. Remove unnecessary dietary restrictions. Do not institute artificial feeding at the end of life as this can prolong dying and cause discomfort.

4. Consider withdrawing feeds and fluids when an actively dying patient is no longer requesting this, has a depressed level of consciousness or has abdominal distension and or nausea/vomiting.

    a. Dehydration is beneficial to the dying process: it decreases secretions and 3rd space fluid loss, cerebral oedema and fluid overload (especially in patients with cardiac or renal failure).

    b. Ketosis induces coma and assists with pain control through the release of endorphins. Ketosis also suppresses hunger (allays family's fears of starvation).

5. Stop unnecessary medication (e.g. supplements and vitamins, enzyme replacement therapy, antibiotic prophylaxis) and focus on medications required to manage distressing symptoms or ensure comfort.

6. Use alternative routes of administering medication if patient is unable to swallow, e.g. buccal, subcutaneous or nebulised.

7. Ensure ongoing good nursing care including skin and mouth care. Use ripple or eggbox mattress as patient becomes less able to turn in bed. This also decreases the need for disruptive 2 hourly position changing.

8. Be prepared to manage sudden (especially traumatic) end of life events. Warn staff/family about the possibility and have appropriate drugs and equipment ready.

9. Stop unnecessary vital sign monitoring in hospitals when death is imminent. Watching "deterioration by numbers and sounds" can be distressing for family.

10. Improve access to the patient by removing NGTs, drips, oxygen etc., if not providing comfort), and allow relatives direct and intimate contact with their loved ones. Allow for privacy in a separate room if at all possible.

11. Try ensuring that someone is always present at the bed side of the dying person if at all possible. A significant fear of many children and adults is dying alone.

12. Don't delay formal certification of death and make sure you sensitively announce that the patient has died, don't assume the family knows. Prepare the body for viewing (remove tubes, clean face and linen). Warn family about immediate post death changes (e.g. muscle twitches, passing of flatus, and expectoration of air).

13. Allow sufficient time for family to say their last farewells and to perform any religious or cultural practices before the body is laid out and taken to the mortuary. Some religious groups need to be involved in the washing and preparation of the body for burial. If death occurs at home in the middle of the night there is no urgent need (unless this is too distressing for the family) to remove the body until morning.

14. Provide assistance with disclosure to siblings of deceased children, if requested, and especially if they were not prepared beforehand.

15. Complete the necessary administrative processes (death notification, certification, cremation forms) timeously.

BEREAVEMENT SUPPORT

Care should not end with the death of the patient especially where CF care providers have walked a long journey with the patient and their family. The loss of relationship with this team adds to the bereavement experience. The decision to go to the funeral of a patient is a uniquely individual one and appreciated by families who extend invitations to healthcare professionals to attend. Parents and siblings at risk for complicated grief (e.g. death sudden, traumatic, unfinished business, conflictual or complicated relationship with the deceased) should be identified and support offered. Some families appreciate a follow up visit with the treating clinician to discuss events that happened at the end of life. Ongoing grief support by CF team social workers or referral to other organisations offering this may be needed.

RESOURCES

- Hospice Palliative Care Association of South Africa (HPCA): https://www.hpca.co.za/
- Palliative Treatment for Children - South Africa (PATCH-SA): http://patchsa.org/

APPENDIX A: FORMULARY

1. ANTIMICROBIALS:

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

Antibiotic	Route	Paediatric dosage	Adult Dosage	Comments
Amikacin	Intravenous	30-35mg/kg OD	30-35mg/kg OD	Peak and trough levels to be done
	IV solution nebulised	<12y:250mg BD	500mg BD	Dilute with 4ml of saline
Amoxycillin	Oral	50-100mg/kg daily in divided doses	1gram TDS	
Amphotericin	Nebulised	10mg BD or QID or 25mg BD	10mg BD or QID or 25mg BD	Dissolve with water for injection
	Intravenous	1mg/kg then increase 5mg/kg/d over 3 days	1mg/kg then increase 5mg/kg/d over 3 days	Give test dose 100ug/kg over 10min observe 30min LFT and UKE 3x/week
Liposomal amphotericin	Intravenous	100ug/kg (max1mg) test dose Day 1:1mg/kg 24hourly Day 2: 2mg/kg 24hourly 3mg/kg 24hourly	100ug/kg (max1mg) test dose Day 1:1mg/kg 24hourly Day 2: 2mg/kg 24hourly 3mg/kg 24hourly	
Anidulafungin	Intravenous	Day 1: 2-4mg/kg Day 2:1-2mg/kg OD	Day 1: 100-200mg Day 2: 50-100mg	
Azithromycin	Oral	1)10mg/kg OD (max 500mg) 2) 10mg /kg daily 3 x week e.g. Monday, Wednesday, Friday	500mg OD 500 mg 3 x weekly	1) Treatment for NTM, atypical infections e.g. mycoplasma2) Prevention of exacerbations in symptomatic individuals or chronic Pa infection
Caspofungin		70mg/m^2 (max 70mg) loading dose then 50mg/m^2 (max 70mg) OD	<80kg: 70mg loading dose then 50mg OD >80kg: 70mg daily OD	
Cefazolin	Intravenous	50-100mg/kg/day in 3-4 divided doses	1.5g QID or 2g TDS	Max 6g/day

Cefepime	Intravenous	150mg/kg/day	2g TDS or continuous infusion 2g IV over 30-60 minutes and then 2g IV 8-hourly, infused as a continuous infusion x 14/7	Max 6g/day See Appendix on continuous infusions
Cefotaxime	Intravenous	50mg/kg TDS or BD	2g TDS	Max 12g in 24hours
Cefoxitin	Intravenous	<12y:40mg/kg BD	2-3gram BD	MAC infection
Ceftazidime	Intravenous	50mg/kg (max 3gram) BD or TDS (max3g/dose) or continuous infusion	2-3gram (max 8g/d) TDS or 2g IV over 30-60 minutes and then 2g IV 8 hourly, infused as a continuous infusion x 14/7	
	Nebulised	1 gram BD	1 gram BD	*B. cepacia* infection Dilute with 3ml of water for injection
Cefuroxime	Intravenous	50mg/kg BD or TDS	750mg-1.5g TDS	Max 2gram
	Oral	15mg/kg BD	500mg BD	
Cephalexin	Oral	25mg/kg QID	1-2gram in 2-4 divided doses	
Ciprofloxacin	Oral	1m-5y: 15mg/kg BD 5-18y: 20mg/kg BD (max 750mg)	750mg (max 2g) BD	
	Intravenous	30mg/kg/day TDS or BD	400mg TDS or BD	Max 1.2gram/day
Clarithromycin	Oral	<12y: 7.5-15 mg/kg BD	>12y: 250-500mg BD	NTM infection, atypical infections
Clindamycin	Oral	1m-18y:5-7mg/kg/dose (max600mg) QID	600mg QID	Take with plenty of water
	Intravenous	30-40mg/kg/day TDS or QID	2.7g/day TDS or QID	
Cloxacillin	Oral or IV	25-50mg/kg QID	1-2g QID	
Co-amoxy-clavulanate	Intravenous	30 mg/kg under 12 years 8 hourly	1.2g 6-8 hourly	
	Oral	4:1 ratio <20kg 15-25mg/kg/dose TDS 7:1 20-30mg/kg BD	4:1 ratio 500/125mg TDS 7:1 875/125mg BD	

		16:1 (ES formulation) 30-50mg/kg BD	16:1 (SR) 2 000mg/125mg BD	
Colomycin	Intravenous	40 000U/kg TDS	2MU TDS	Bolus dosage 2MU in 10ml 0.9% saline over 5min if
	Nebulised	30000-60000U/kg BD or TDS	1-2MU	BD Dilute 4ml saline
Co-trimoxazole	Oral	6w-6m:120mg BD 6m-6y:240mg BD 6-12y:480mg BD	>12y:960mg BD	
	Intravenous	<12y: 250mg/m^2 stat then 150mg/m^2 TDS	>12y: as paed but BD	Mix in 5%Dextrose
Doxycycline	Oral	12-18y:200mg loading dose then 100-200mg OD	200mg OD	*Burkholderia*
Erythromycin	Oral	<2y: 125 mg QID 2-8y 250 mg QID	>8y:1-2/g/day QID	
Flucloxacillin	Oral	25-50 mg/kg QID <18y (may be divided 3 dosages)	1-2gram QID	on empty stomach
Fluconazole		1m-18y: 6-12mg/kg (max 400mg) OD	400mg OD	
Gentamycin	Intravenous	10-12mg/kg OD	Max 480mg OD	Peak and trough levels
	Nebulised IV solution (80mg/2 ml)	<5y: 40mg BD >5y: 80-160mg BD	160mg BD	Dilute with 4ml saline
Hypertonic saline	Nebulised	2-4ml of 3%, 5% or 7% solution BD	2-4ml of 3%, 5% or 7% solution BD	Up to 30 min prior to physiotherapy
Imipenem	Intravenous	<40kg: 60-100mg/kg/d as TDS infusion or continuous infusion	>40kg: 0.5g-1g TDS 1g IV over 30 – 60 minutes and then 1g IV 6 hourly, each dose infused over 2 hours x 14/7	Max 4gram daily
Itraconazole	Oral	5mg/kg BD	200mg (Max 400mg) BD	
Levofloxacin	Oral/ Intravenous	10-20mg/kg/day BD or OD	750mg BD or OD	
Linezolid	Oral/ Intravenous	1m-12y: 30mg/kg/day TDS (max 600mg)	600mg BD	
Meropenem	Intravenous	20-40mg/kg TDS or continuous infusion	2g TDS 2g IV over 30 –60 minutes, then 2g IV 8 hourly, each dose infused	Max 6g/day

			over 3 hours x 14/7	
Minocycline	Oral	4mg/kg stat then 2mg/kg BD	200mg stat then 100mg BD	
Piperacillin-Tazobactum	Intravenous	100mg/kg TDS or QID or Continuous infusion	2-4g TDS or QID 4.5g IV over 30 – 60 minutes and then 9g IV 12 hourly infused as a continuous infusion x 14/7 Or 18g IV every 24 hours infused as a continuous infusion x 14/7	Max 16g/day
rhDNase/Pulmozyme®	Nebulised	>5y: 2.5mg OD or BD	2.5mg OD or BD	>30 min before physiotherapy Keep refrigerated Do not dilute
Rifampicin	Oral	1m-1y:5-10mg/kg OD 1-18y:10mg/kg OD (max450mg<50kg, max 600mg>50kg)	600mg OD	BD with Staph infection Usually in combination other antibiotics to prevent resistance, 30min-1hr prior to meal For treatment of MRSA, TB
Salbutamol	Nebulised/MDI	6m-5y: 2.5mg QID >5y: 5mg QID	5mg up to QID	
Sodium fusidate	Oral	1y-1m:15mg/kg TDS 1-5y:250mg TDS 5-12y:500mg TDS	500mg sodium fusidate or 750mg fusidic acid (doubled for severe infections) TDS	With or after food traditionally combined e.g. flucloxacillin for resistance (Asymptomatic *Staph* or minor exacerbations)
Teicoplanin	Intravenous	10-20mg/kg/d Loading dose 10mg/kg	6-12g/day (400mg/dose initially)	BD first 3 doses then OD
Tigecycline	Intravenous	2mg/kg over 1 hour stat then 1mg/kg over 30min BD	100mg stat over 1hour then 50mg over 30min BD	
Tobramycin	Intravenous	10mg/kg OD	10mg/kg OD	Max starting dose 660mg Trough levels needed
	Nebulised IV solution (80mg/2 ml)	5-10y: 80mg BD	>10y:160mg BD	Dilute with 4ml saline

	Nebulised inhalational solution (300mg/5ml) (Tobi®)	300mg BD	300mg BD	After physiotherapy Undiluted
Vancomycin	Intravenous	30mg/kg stat then 15-20mg/kg TDS or BD	30mg/kg stat then 15-20mg/kg TDS or BD	Max initial dose 1.25g Target serum level 15-20ug/ml
	Nebulised IV solution (500 or 1g /10 ml)	250mg/4ml over 10mins BD	250mg/4ml over 10mins BD	*MRSA* and *S.aureus*
Voriconazole	Oral	<40kg: 9mg/kg BD	>40kg Load 400mg BD x2 then 200-300mg BD	Photosensitivity ABPA Monitor LFT Interactions with other meds

2. GASTROINTESTINAL MEDICATIONS

Meconium ileus/DIOS:	Paediatric Dosage	Adult Dosage	Comments
Golytely / Kleen-prep **Picoprep/Coloprep**	1 sachet to 1L water- can flavour with clear cordial 1 sachet in 250ml 1 sachet 12hrs apart	1 sachet to 1L water- can flavour with clear cordial 1 sachet in 250ml 1 sachet 12hrs apart	Given orally or via NG tube. Start rate 10-15ml/kg/hr (2cups) up to 25ml/kg/hr, maximum 1L/hour Maximum volume 100ml/kg or 4lL over 4 hours until clear fluid passed per rectum. Monitor for hypoglycaemia. Stop if vomiting Repeat next day if not clear
Pegicol (7g) ® **Movicol (14g)**	1-5 years: Pegicol® 5-10 years: Pegicol® or Movicol® Over 10 years: Movicol®	Movicol®	Mix 1 sachet Pegicol® with 60ml water Start 2 sachets/day, increase by 2 daily until clear Mix 1 sachet Movicol® with 125ml water Give 2-4 sachets daily for 2-5 days for impaction, give total amount over maximum 4-6 hours daily (can mix 4 sachets in 500ml water)

Constipation:			
Lactulose	1-5years: 5ml BD 5-10years: 10ml BD >10years: 15-20ml BD	15-20ml BD	Adjust dose according to response
Pegicol(7g) ® **Movicol(14g)**	1 - 5 years: 1-2 sachet of Pegicol daily. Maximum 4 sachets daily. 5 - 10 years: 2 sachets of Pegicol OD. Maximum 4 sachets daily. 10 - 18 years: 1-2 Movicol (14g) sachets daily.	1-2 sachets Movicol (14g) daily	Used in chronic constipation to prevent faecal impaction. Mix Pegicol with 60ml water. Mix Movicol with 125ml water
Acid suppression			
Esomeprazole	0.4-0.8mg/kg OD	20mg-40mg OD or BD	Sachets for 2.5mg; 5mg;10mg Mix sachet with 15ml water, stir until granules dispersed, use within 30min
Lansoprazole	1.5mg/kg OD	30mg OD	
Omeprazole	0.7-1.4mg/kg/d Losec Mups® 10mg	20mg	Swallow whole or open capsule and mix contents with fruit juice or milk Dissolve Mups dispersible tablets in tablespoon of water and give immediately
Liver disease			
Ursodeoxycholic acid	20mg/kg/day BD or TDS	200mg-400mg BD	Take with or after food. Rare side-effect is diarrhoea

3. MICRONUTRIENT SUPPLEMENTS

Recommended daily doses for supplementation.

Note: 5ml standard KiddiVit syrup contains 3 000U vitamin A and 400U Vitamin D3

AGE	VITAMIN A	VITAMIN D3	VITAMIN E	VITAMIN K
	1mcg=3.3IU	1mcg=40IU	(200u = 134mg)	(2mg/0.2ml)
< 1YEAR	1 000-4 000 IU	400-1 000 IU	10 – 100 IU	2-5mg
>1YEAR	4 000 – 10 000 IU	400-2 000 IU	100-400 IU	5 mg
ADULTS	4 000-10 000 IU	800-2 000IU	100 – 5OO IU	10 mg

0.6ml MVT drops (Kiddivit) contains 3 000IU vitamin A and 400IU vitD3
Ergocalciferol (vitamin D) contains 5 000u/ml
Calciferol 50 000U tablet can be given weekly or 2 weekly
1 alfa Vitamin D available in 0.25microgram and 1 microgram capsules
Vitamin E capsules 400U (approximately 10 drops, 3 drops=100U, can give 400U Monday/Wednesday/Friday))
Vitamin K (injectable Konakion) 2mg/0.2ml solution or 10mg un-scored tablets

APPENDIX B NUTRITIONAL PRODUCTS

ORAL NUTRITIONAL SUPPLEMENT [ONS]

Type of Product	1-10 years		Over 10 years	
Standard **[1.0kcal/ml]**	**Product Name[Company]**	**Unit size**	**Product Name[Company]**	**Unit size**
	Pediasure [Abbott]	400g tin /850g tin 200ml bottle	Fresubin Original [Fresenius Kabi] Fresubin Fibre powder	200ml bottle 500g
	Replace Jnr LGF [Nativa]	400g tin	Ensure [Abbott]	400g tin
	Nutrimil Jnr [Diva]	1kg bag	Nutren Fibre [Nestle]	400g
			Nutren Optimum OR Nutren Activ [Nestle]	400g
High energy drink **[1.5kcal/ml]** ***Indication:*** ***Higher calories in smaller volume***	Frebini Energy Fibre [Fresenius Kabi]	200ml	Fresubin Energy Fibre [Fresenius Kabi]	200ml
	Nutrini drink [Nutricia] ready-to-drink and powder	200ml & 400g tin	Fortisp [Nutricia]	200ml
			Ensure Plus [Abbott]	200ml
			Fresubin Jucy [Fesenius Kabi]	200ml
			Enlive Plus [Abbott]	200ml
			Fortijuice [Nutricia]	200ml
Very high energy/protein drink **[2.0kcal/ml]** ***Indication:*** ***Higher calories in smaller volume***	**Adults products [>10years of age]**			
	Fresubin 2kcal Drink [Fresenius Kabi]		200ml	
	Fresubin 2kcal Crème [Fresenius Kabi]		125g cup	
	Scandishake [Nutricia]		85g sachet	
Other specialised ***Only under medical supervision***	Supportan [Fresenius Kai]		200ml	
	Glucerna [Abbott]		400g tin	
	Diasip [Nutricia]		200ml	
	Diben [Fresenius Kabi]		200ml	
	Fresubin Thickened Stage II [Fresenius Kabi]		200ml	

MODULARS – SUPPLEMENTS TO ENRICH FOOD OR NUTRITIONAL PRODUCTS [ONLY UNDER MEDICAL SUPERVISION]

	Component	Unit size	Manufacturer
Carbohydrate supplement	Polycose	400g	Abbott
	Fantomalt	400g	Nutricia
	Replace Carbohydrate	400g	Nativa
Protein supplement	Protifar	225g	Nutricia
Fat supplement	MCT oil	500ml bottle	Nutricia
	Calogen	200ml bottle	Nutricia
	Liquigen	200ml	Nutricia
Combined Fat and Carbohydrate	Duocal SS	400g tin	Nutricia
	Fresubin 5kcal shot	120ml	Fresenius Kabi

INFANT PRODUCT RANGE

Type of Product	Infants [0-12 months]	
High energy product **[1.0kcal/ml]**	**Product Name [Company]**	**Unit size**
	Infatrini [Nutricia] Ready-to-drink And powder	125ml bottle 400g tin
Extensively hydrolysed **[0.67kcal/ml]** ***Indication:*** ***Proven malabsorption***	Pepticate [Nutricia]	400g tin
	Alfare [Nestle]	400g tin
	Similac Alimentum [Abbott]	400g tin or 946ml
	Pepti-K [Kairos]	100ml or 275ml
Other specialised products ***Only under medical supervision***	Neocate [Nutricia] 400g tin	

PAEDIATRIC AND ADULT RANGE OF ENTERAL NUTRITION PRODUCTS

Type of Product	1-10 years		Over 10 years	
Standard **[1.0kcal/ml]**	**Product Name[Company]**	**Unit size**	**Product Name[Company]**	**Unit size**
	Pediasure [Abbott]	400g tin /850g tin 500ml bottle	Fresubin Original [Fresenius Kabi] Fresubin Fibre powder	500ml bottle 500g
	Replace Jnr LGF [Nativa]	400g tin	Ensure [Abbott]	400g tin
	Frebini Original	500ml bag	Nutren Fibre [Nestle]	400g
	Nutrini MultiFibre [Nutricia]	500ml bag	Osmolite [Abbott]	500ml
High energy drink **[1.5kcal/ml]** ***Indication: Higher calories in smaller volume***	Frebini Energy Fibre [Fresenius Kabi]	500ml bag	Fresubin Energy Fibre [Fresenius Kabi]	500ml
	Nutrini Energy [Nutricia]	500ml bag	Nutrison Multi Fibre [Nutricia]	1 000ml
			Jevity Plus [Abbott] [1.2kcal/ml]	1 000ml
Extensively hydrolysed **[1.0 -1.5kcal/ml]** ***Indication: Proven malabsorption***	Nutrini Peptisorb [Nutricia]	500ml	Survimed [Fresenius Kabi]	500ml
	Peptamen Jnr [Nestle]	400g tin	Nutrison advance Peptisorb [Nutricia]	1 000ml
	Peptamen Jnr Advance [Nestle]	500ml bag	Peptamen Prebio [Nestle]	250ml
			Alitraq [Abbott]	76g sachet
Very high energy/protein drink **[2.0kcal/ml]** ***Indication: Higher calories in smaller volume***	**Adults products [>10years of age]**			
	Fresubin 2kcal Drink [Fresenius Kabi]		200ml	
	Scandishake [Nutricia]		85g sachet	
Other specialised products ***Only under medical supervision***	Supportan [Fresenius Kai]		200ml	
	Glucerna [Abbott]		400g tin	
	Diasip [Nutricia]		200ml	
	Diben [Fresenius Kabi]		200ml	

APPENDIX C: CYSTIC FIBROSIS ASSOCIATION

SOUTH AFRICAN CYSTIC FIBROSIS ASSOCIATION (SACFA)

SACFA EXECTUVE COMMITTEE

Alain d Woolf - President
082 771 7779
info@adwman.com

Alan Dunn - Treasurer
083 285 5853
alandunn@gmail.com

Secretary - Ashleigh Robertson
071 602 2966
info@cysticfibrosis.co.za

There are three regional associations, which are registered NPO's:

- Cystic Fibrosis Association Central Region (Gauteng)
- KZN Cystic Fibrosis Association
- Cape Cystic Fibrosis Association

The regional associations have been in existence for over 30 years, and have 3 main objectives:

- To provide emotional support to families when their child has been diagnosed with cystic fibrosis.
- To promote early diagnosis and so have a positive impact on the progression of the disorder.
- To ensure that all those with cystic fibrosis receive proper treatment.

NATIONAL STRUCTURES

The regional structures came into existence before the national body was formed, and therefore most activities are driven by the regional bodies, with the national body (SACFA) being more of an umbrella body, which monitors regional developments and handles issues which need to be addressed at national level. The Medical & Scientific Advisory Committee for cystic fibrosis (MSAC) was formed under the auspices of SACFA. MSAC is an active and representative panel of experts in various aspects of CF management, welfare and research.

SUMMARY OF FUNDING REQUIREMENTS

- Support of the CF clinics around the country, which are open to anyone with CF
- Sponsoring essential equipment for daily use by patients with financial constraints
- Promoting public awareness, thus facilitating early diagnosis
- Supporting the work done by MSAC

CONTACT DETAILS FOR REGIONAL ASSOCIATIONS

- Cystic Fibrosis Association Central Region (Gauteng): Alan Dunn 083-285-5853 alanfdunn@gmail.com
- KZN Cystic Fibrosis Association: Ashleigh Robertson 071-602-2966 info@cysticfibrosis.co.za
- Cape Cystic Fibrosis Association: Tarryn Tweedie 082-417-5861 cf.tarryn@gmail.com

Website http://www.sacfa.org.za
All clinic contact details are available on the website