

CLINICAL GUIDELINES

Care of adults with cystic fibrosis 2013

Royal Brompton & Harefield 
NHS Foundation Trust

www.rbht.nhs.uk/cystic-fibrosis

ADULT ROYAL
CYSTIC BROMPTON
FIBROSIS HOSPITAL
CENTRE LONDON

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Contributors to this edition

Thanks go to Dr I Balfour-Lynn for his generosity in letting us use the paediatric guidelines as a template. This edition of the adult guidelines has been written by members of the Royal Brompton Hospital Adult Cystic Fibrosis Multidisciplinary team, specifically:

Diana Bilton, Nick Simmonds, Khin Gyi, Margaret Hodson, Su Madge, Milly Dack, Alan Peres, Linda Thrift, Susan Talbot, Penny Agent, Helen Parrot, Gemma Morgan, Kate Rowland-Jones, Jane Wood, Anne-Marie Doyle, Elaine Bowman, Mami Harrison, Keith Thompson, Bela Sood

These guidelines are based on published evidence as well as the extensive clinical experience of the Adult CF Team. This is how we do things, but it does not mean that other regimens are necessarily wrong just because they are different. However patients, who come to the Royal Brompton Hospital, will be looked after using these guidelines.

1: INTRODUCTION

The purpose of this document is to set out guidelines to ensure a standard approach to care for adults with Cystic Fibrosis (CF) looked after at the Royal Brompton Hospital. The Adult CF Service is a specialist CF Centre as designated by the CF Trust Clinical Standards 2011. Specialist centre care at the Royal Brompton Hospital offers access to comprehensive care from a multidisciplinary team consisting of consultant specialising in CF, junior doctors, clinical nurse specialists, dietitians, physiotherapists, clinical psychologists, pharmacists and a welfare rights advisor. The document is written by the expert CF multidisciplinary team at the Royal Brompton Hospital for use by any staff involved in caring for adults with CF. It also serves as a guide for the adults attending the Royal Brompton CF Service. We are delighted if it provides information for others interested in CF care.

The service for adults with CF was founded at the Royal Brompton Hospital in 1965 by Sir John Batten. Since that time the service has grown under the leadership of Professor Hodson and Professor Geddes to the largest clinic in Europe caring for 600 adults. The Brompton team led the way in terms of multidisciplinary team working for adult CF care and were responsible for the introduction of many innovations which we regard as routine today. As survival increases and our paediatric colleagues refer 16 year olds with lung function in the normal range, it is now our challenge in the second decade of the third millennium to ensure we continue to enhance care and improve outcomes for adults with CF, ensuring that each individual receives expert advice and treatment tailored to their particular needs.

1.2 AIMS OF THE SERVICE

The aims of the Adult CF Service are to seek to maintain or improve lung function and nutritional status to as near normal as possible, thus enhancing survival. We aim to do this in a targeted approach whilst seeking to optimise quality of life, and supporting our patients with CF in reaching their career and lifestyle goals. We aim to be the expert advice team providing input on how to manage CF through all the different phases of adult life from “my first holiday abroad without my Mum and Dad” to “going to University” and “planning a pregnancy”. We expect the 16 year olds with CF graduating to the adult service to have thoughts and plans for their future and our transition services are carefully planned to allow families to plan the move to the adult unit at a convenient time between age 16 and 17 years.

In common with all CF services in the UK we want to see patients every 3 months as a minimum in the outpatient clinic with the full team, and perform a full annual review once a year. We average 20 to 25 CF adults as inpatients at any one time on Foulis Ward, in single rooms with en suite facilities. Our aim is to try and keep people with CF out of hospital and getting on with life, by ensuring the best and latest chronic therapies are available. The home intravenous antibiotic service we provide does allow people to have treatment and stay at college or work where possible, safe and sensible.

1.3 RESEARCH AND REGISTRY

The Royal Brompton’s Adult CF Unit has led the way in researching new treatment for CF, including nebulised antibiotics, DNase (Pulmozyme) and independent physiotherapy techniques. We wish to remain at the forefront of new development and as a designated European Cystic Fibrosis Society Clinical Trials Site are offered opportunities to recruit adults with CF into trials of new treatments. In addition we strongly believe in auditing our outcomes and ensuring we learn from experience. As a result we ask all our patients to sign up

for their anonymised data to be recorded on the UK CF registry run by the CF Trust. In that way we can learn the most about the long-term effects of the introduction of different treatment approaches.

2: STAFF AND CONTACT DETAILS

Department of Cystic Fibrosis

Royal Brompton and Harefield Foundation Trust
Sydney Street, London SW3 6NP

Royal Brompton Hospital switch board: 020 7352 8121

Consultants

Dr Diana Bilton	Consultant (Centre Director)	
Angela Howard	Secretary	ext 8182

Dr Nicholas Simmonds	Consultant	
Judith Charlton	Secretary	ext 8997

Dr Khin Ma Gyi	Consultant	
Judith Charlton	Secretary	ext 8009

Infection & NTM Disease

Dr Michael Loebinger	<i>Attends Monday afternoon CF clinic</i> Consultant	
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Trust Physician – Cystic Fibrosis

Dr Barbara Belkarty		Bleep 7047
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Specialist Nursing Team

Dr Susan Madge	Consultant Nurse	cfhomecare@rbht.nhs.uk ext 4053
Milly Dack	Clinical Nurse Specialist	ext 8065
Linda Thrift	Clinical Nurse Specialist	ext 8065
Alan Peres	Clinical Nurse Specialist	ext 8065
Susan Talbot	Clinical Nurse Specialist	ext 8065
Zoe Hallett	Administrator / annual review coordinator	ext 8065

Registry Nurse Coordinator

Juliana Burgess	Registry Nurse Coordinator	ext 4935
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Research Nurses

Dr Sandra Scott	Senior Research Nurse	ext 4068
Myril Mariveles	Research Nurse	ext 4401

Specialist Physiotherapy Team

Penny Agent	Deputy Director Rehabilitation & Therapies	ext 8056
Helen Parrott	Clinical Specialty Lead - Adult CF	ext 8088
Gemma Stanford	Specialist CF Physiotherapist	bleep 7310
Fiona Shaw	Specialist CF Physiotherapist	bleep 7302

Specialist Dietetic Team

Sarah Collins	Specialist CF Dietitian	bleep 7102
Kate Rowland-Jones	Specialist CF Dietitian	bleep 7100
Annika Woodcock	Specialist Adult CF Dietitian	bleep 7555

Clinical Psychology & Psychiatry Team

Dr James Woolley	Consultant in Liaison Psychiatry	ext 4450
Dr Anne-Marie Doyle	Consultant Clinical Psychologist	ext 4014
Oonagh Koppel	Clinical Psychologist	ext 8060
Nicos Nicolaou	Psychiatric Liaison Nurse	ext 8060

CF Pharmacistsrbh-tr.RespiratoryPharmacy@nhs.net

Elaine Bowman	Specialist Pharmacist	ext 8059
Mami Harrison	Specialist Pharmacist	ext 8059
Keith Thompson	Specialist Pharmacist	ext 8059

Foulis Ward

Viv Green	Ward Manager	ext 8069
Carol Wingett	Welfare Rights Advisor	ext 4736
Ward registrar		bleep 1011

Patient Support

Kevin Passey	Patient Advocate	01798 815741
Emma Lake	Expert Patient Advisor (CF Trust)	elake@cftrust.org.uk

2.1 SPECIALISTS WITH CF EXPERTISE**Microbiology****Royal Brompton Hospital**

Dr Khalid Alshafi

Palliative / Symptom Care**Royal Marsden Hospital** *Attends Wednesday MDT*

Dr Jane Wood

Dr Joy Ross

Jenny Wright

Clinical Nurse Specialist

Gastroenterology

Dr David Westaby

Dr Alan Steele

Hammersmith Hospital**Chelsea & Westminster***Monthly Specialist GI clinic at RBH**Monthly Specialist GI clinic at RBH***Ear Nose & Throat**

Mr Saleh

Royal Brompton Hospital*Tuesday morning clinic at RBH***Endocrine**

Dr Kevin Shotliff

Dr Nicola Bridges

Chelsea & Westminster*Monthly CF Clinic RBH Thursday***Obstetrics & Gynaecology**

Mr Guy Thorpe-Beeston

Chelsea & Westminster**Interventional radiology**

Dr Simon Padley

Royal Brompton Hospital

Allergy Prof Steven Durham	Royal Brompton Hospital	<i>Tuesday morning clinic RBH</i>
Rheumatology Dr Alex Brand	Chelsea & Westminster	
Dermatology Dr Nilesh Morar	Chelsea & Westminster	<i>Clinic once a fortnight RBH</i>
Neurology Dr John Janssen	Chelsea & Westminster	<i>Wednesday afternoon clinic RBH</i>
Thoracic surgery Mr Michael Dusmet Mr Simon Jordan	Royal Brompton Hospital	

3: THE SPECIALIST CF SERVICE

3.1 CLINICS

Clinic segregation is routine at all clinics where patients are given a room for the duration of the visit and the team (physiotherapist, dietitian, clinical nurse specialist, and doctor) see all patients in their allocated rooms individually. At each clinic sputum is collected and spirometry, weight and height (plus BMI) are measured. Additionally Portacaths can be flushed where necessary. When patients are unwell IV antibiotics can be commenced in clinic or on Lind ward – patients must stay for one hour after the first dose (see section 3.4.1).

Segregation Policy at the Royal Brompton

- The adult CF clinic also divides each clinic by sputum microbiology.
 - ‘A’ clinic – for everyone who grows *Pseudomonas aeruginosa* and other gram negative bacteria (apart from *Burkholderia cepacia* complex) in their sputum
 - ‘B’ clinic – for people who do not grow *Pseudomonas aeruginosa* in their sputum
 - ‘C’ clinic – for people who grow *Burkholderia cepacia* complex in their sputum
- Clinics are held on Monday (outpatients east), Tuesday and Friday (outpatients west) afternoons.
- The C clinic is held monthly on a Friday. The A and B clinics are on Mondays and Tuesdays on a rotating basis and on the Fridays when there is not a *Cepacia* clinic. This allows us to fit patients in to clinics urgently during any given week according to microbiological status.
- Patients are encouraged to arrive at their appointment time to reduce risks of cross infection.

Other clinics also held include

- CF related diabetes clinic— last Thursday in the month
- Gastrointestinal clinic—4th Friday in the month
- Difficult CF Diagnosis Clinic – 2nd Thursday morning of alternate months
- Sweat test clinic – Every Thursday morning except the last Thursday in the month

3.1.1 Doctors in clinic

There is always at least one consultant in clinic (and usually two). In addition there will be a research fellow (a doctor working on CF related research and being trained for 2 or 3 years in specialist CF clinics) as well as a respiratory registrar who usually works in CF for 6 months.

At the beginning of each clinic prior to the first appointment there is a 30 minute team meeting to discuss the patients attending that clinic. During this meeting the consultants check which patients should be seen by them and which patients can be allocated to a fellow or registrar. The fellow or registrar can discuss decisions with the consultant during the clinic.

All patients returning for an annual review follow-up consultation will be guaranteed to see a consultant.

Consultant rota for clinics

Monday pm	Dr Bilton	Dr Gyi	Dr Loebinger
Tuesday pm	Dr Simmonds	Dr Bilton	

3.1.2 Access to other services

Adults with CF will see the nurse specialist, the dietitian and the physiotherapist at each routine clinic visit. The CF nurse specialist will establish whether there is a need to see the welfare rights advisor or the psychologist and will coordinate this where possible to fit in on the same day. We also try and coordinate extra tests eg: CT scan to fit in with clinic visits.

3.2 ANNUAL REVIEW

The annual review system was designed in 2010 by both the CF team and patients. Initially the CF team had a meeting to discuss how improvements could be made, and then individuals from the CF team spent an annual review day with a number of patients. During this time the CF team discussed with each patient how things could be improved at different points throughout the day. Further discussions and planning led to the two part system we have today (one half day to collect information and one clinic visit).

The first part of the annual review is based on Lind ward and is an information gathering half day of tests and investigations. These include:

- Lung function – spirometry, arterial blood gases, lung volumes and gas transfer
- Chest x-ray
- Blood tests – full blood count, urea & electrolytes, coagulation screen, liver function, vitamins A,D&E, aspergillus ICAP, aspergillus allergen specific IgE, IgA, IgM, total IgE, HbA1C, fasting glucose, CRP, calcium, phosphate, magnesium, chloride, iron, ferritin, cholesterol, transferrin, iron saturation
- Sputum microbiology, including NTM
- Oral glucose tolerance test (for those who do not have CF Related Diabetes)
- Bone density scan if indicated
- Liver or abdominal ultrasounds – if specifically requested
- Chest CT if specifically requested

The day is led by the CF clinical nurse specialists who co-ordinate the process. Each patient spends at least half an hour with the dietitian, pharmacist and physiotherapist discussing areas such as nutrition, CFRD management, medication, physiotherapy techniques, smoking, incontinence and posture. The nurse specialist carries out a physical examination, takes a medical and social history and discusses areas such as health status over the previous 12 months, fertility, contraception, plans to start a family, college, work and plans for future travel.

Approximately four to six weeks later, when all the information has been reported and reviewed by a consultant (blood test results, x-ray report and comments from the CF team etc), patients are invited to meet the consultant at a clinic visit (they do not have to take part in the usual clinic procedure of seeing the CF team). The discussion allows the consultant to spend some time talking to the patient about the previous year and, based on results, make a treatment plan for the next 12 months. This is an opportunity for patients to say what they think, ask questions and contribute their own ideas to the treatment plan. A final report is then written by the consultant and sent to the GP and patient.

3.3 TRANSITION FROM PAEDIATRIC TO ADULT CARE

There are approximately four transition clinics a year with the RBH Paediatric CF Clinic and one or two (depending on numbers) with Great Ormond Street CF Clinic. In addition adolescents transition from other paediatric CF clinics in the London area because of geography or choice. The numbers of patients transitioning to adult care at RBH per year are approximately 20-30.

Transition from paediatric to adult care is discussed with all patients and their families from an early age; however a more detailed discussion takes place from about 14 years onwards. The transition process has been divided into two parts: pre-transition and transition. Invitations to attend a pre-transition clinic are sent to all 15 year olds, this is an opportunity to meet the adult CF team and ask any questions before attending the transition clinic. Invitations are sent for the transition clinic at around 16 years of age; details included with this invitation outline the choices for adult CF care from different centres and information about growing up with CF. The Adult CF Clinic at the Brompton Hospital may not be the CF centre of choice for some patients – advice is given on how to access other centres with contact details for each one. (www.rbht.nhs.uk/cf-transition/)

Transition clinics for patients wishing to transfer their care to the Adult Clinic at RBH aim to make the transition from the paediatric to the adult service easier for both the patient and family. Most patients will transfer at some stage after their 16th birthday, depending on the individual and family circumstances, however the majority will have been through transition by their 17th birthday. A transition document detailing family, social and clinical history is completed by each patient, their family and clinical nurse specialist then given to the adult team in preparation for their transition clinic. There is an optional section entitled 'all about me' which is completed by the teenager. The Transition Integrated Care Pathway (TICP) is part of this document and is commenced at this time.

Transition clinics are held on Monday and Friday afternoons in the usual paediatric clinic area. The adult CF Team (consultant, nurse specialist, physiotherapist and dietitian) attend each transition clinic to give patients and families an opportunity to meet and ask questions about the move to adult care. The adult consultants who attend transition clinics are either Dr Diana Bilton or Dr Nick Simmonds. The adolescents remain under the care of the paediatric team until they are seen for the first time in the adult clinic. This is to avoid confusion if there is a problem, as the paediatric team still know the patient best at that early stage of transition.

After transition adolescents are followed up more closely for a year or two depending on how they settle into the adult service. Following transition clinic the adult nurse specialist takes the names of the patients and arranges their first adult clinic appointment on days that the same doctor, nurse specialist, physio and dietitian are in clinic to ensure continuity. The TICP is continued until after the first adult clinic appointment. A monthly paediatric/adult transition meeting is held to discuss all patients attending the following transition clinic and to discuss issues arising from recently transitioned patients.

If or when patients need admission to Foulis ward, the Chelsea & Westminster Hospital school teachers visit regularly (and liaise with schools and colleges) to continue education for A levels (exams are taken on the ward if necessary), and university / college. The school also provide a careers advisor. A leaflet outlining educational support is available on the ward. There is a book kept in the nurse specialists' office so that any issues for the school can be referred, the teachers check it weekly.

Segregation during admission because of cross infection can be a problem for these young people, as they value support from each other. To help with this a ward blog has been developed to improve communication

between in-patients. At admission every patient (regardless of age) is asked to sign a 'contract of care', which sets out activities expected from patients during admission (including adhering to cross infection policies). In addition there is a list of what patients can expect from the CF team.

3.4 THE SPECIALIST NURSE TEAM

As an advanced nursing team for cystic fibrosis the specialist nurses provide a comprehensive service which incorporates care for patients of all ages both in hospital and at home. The service is provided by a consultant nurse, four clinical nurse specialists and a team administrator/annual review coordinator.

Inpatient services include:

- Ward based patient support, education and advice.
- Long line insertion.
- Coordinating admissions – Foulis/Lind.
- Nurse led annual review service including physical/clinical assessment, treatment decision making and non-medical prescribing, arranging investigations, GP letter, and preparing reports.
- Coordination of transition service (clinics, paediatric/adult team monthly meetings, providing information and education (leaflets, DVDs, posters).
- Coordination of end of life – talking to patients and families, weekly palliative care meetings, liaising with palliative care team/ local hospices/Macmillan nurses/primary care etc.
- Sputum surveillance (all patients) – checking EPR and monthly MDT sputum meetings.
- Lung transplant liaison (with coordinators at Harefield) including patient education, arranging and following up test results etc.

Outpatient services include:

- Attendance at all outpatient clinics providing psychosocial support, advice and education, dealing with practical issues.
- Running the adult sweat testing service.
- Dealing with patient related telephone calls and emails, including clinical assessment over the phone, non-medical prescribing and liaising with GPs.
- Managing the home IV service (patient education, monitoring aminoglycoside levels –as day case/homecare/postal, follow up post IVs).
- Coordination of CF related diabetes service, outpatients, Continuous Glucose Monitoring Surveillance (CGMS) service, patient education (ie how to inject, care of/use of insulin, how to record blood sugars etc), psychosocial support etc.

Outreach services include:

- Weekly telephone clinic.
- Close liaison with primary healthcare teams e.g. contact (fax and phone) with GPs about changing treatment.
- Weekly outreach meetings – to decide which patients should be visited at home and which should be included in the telephone clinic.
- Outreach (with physiotherapists) – including work place and college (eg post admission follow-up, monitoring during home IV therapy, end of life, pre/post natal care, clinical assessment, education, bereavement visits).
- Coordinating monthly Portacath flushes – home or hospital.
- Writing letters on behalf of patients – housing, DLA, travel, college.

3.4.1 Home intravenous antibiotics

The clinical nurse specialists coordinate the home IV antibiotic service. All doctors starting patients on home IVs must contact the nurse specialists to arrange aminoglycoside levels and follow-up. Home IV therapy is not available for all patients; suitability must be discussed prior to offering the service to patients.

- The first dose of both antibiotics must always be given in hospital every time.
- Any patient wishing to undertake home IV therapy must be carefully selected and be discussed with the nurse specialist or consultant before any decision is made.
- Patients must be able to follow instructions provided, be fully aware of the treatment burden and be happy to carry this out.
- Home IV therapy is optional and never compulsory, patients must not be pressurised and must be happy to undertake the task. In addition they must be confident of being able to continue with other aspects of the treatment i.e. extra physiotherapy and attention to diet.
- Patients who have carried out home IVs in the past should be asked each time whether or not they are happy to do so again. In particular if there has been a long gap, consideration needs to be given to training needs.
- Patients must complete home IVAB training each time and be signed off on the following:
 - IV line - to look for leaks and signs of infection/thrombosis.
 - Infection control.
 - Allergic reactions - what to look for and to stop drug immediately and seek medical advice.
 - Drug administration and importance of correct timing (especially for aminoglycosides).
 - Use of delivery device (where applicable). This is the collapsible infusion device used by the home delivery company.

Patients must have their 1st dose of antibiotics in hospital and be observed for side-effects for at least one hour before they are discharged home. Before discharge the following MUST be arranged:

- Consent and competency form should be signed and placed in the notes.
- Inform clinical nurse specialists.
- Aminoglycoside levels must be arranged and booked.
- Follow up must be arranged in clinic or on Lind ward.

EPIPENS

It has been advised by the CF Trust that all patients who receive a full course of IV antibiotics at home should have an *Epipen*.

At the Royal Brompton Hospital, we insist that the 1st dose of any antibiotic is given in hospital. Symptoms indicating a reaction to an antibiotic may be delayed, sometimes 48-72 hours later, usually in the form of a maculopapular exanthema or urticaria. Patients are taught to watch for these symptoms during their IV training, they are given instructions to follow if this occurs. In the UK, the practice of prescribing an *Epipen* to all patients having home IV antibiotics is not common. We must stress that it is our practice and recommendation that the 1st dose is always given in hospital, therefore *Epipens* are not routinely prescribed for patients to have at home.

3.4.2 PORTACATHS (Totally implantable venous access devices)

Indications - recurrent problems with venous access in the setting of need for recurrent courses of IV antibiotics. It is not a solution for needle phobia because needle insertion is still required monthly for flushing.

Site of insertion – most often via a subclavian vein into the SVC. The port is usually buried on the upper lateral chest, away from the shoulder joint and breast tissue. Ideally it should be on the non-dominant side. Patients should see the interventional radiologist before the procedure to discuss the procedure and placement. If the patient has had previous central neck lines, imaging of the neck (Doppler ultrasound or MR venogram) may be required to identify a suitable site for insertion.

Protocol for insertion – consent will be obtained by the person performing the procedure. Investigations: CXR, full blood count, coagulation including thrombophilia screen, U&E, group & save. If the thrombophilia screen is abnormal, discuss with Consultant and Haematologist. Ports are not routinely replaced after 5 years (manufacturers advice) if they are in a good position with no complications. Ports are only removed if problems develop such as infection, line blockage or complications such as leakage or re-positioning. Records are kept of all port insertions, port flushes, complications and removal to allow audit to take place.

Insertion – most of the ports are placed under local anaesthetic by an interventional radiologist (Dr Simon Padley Royal Brompton and Chelsea & Westminster Hospital). If it is necessary to place the port surgically then Mr Michael Dusmet and Mr Simon Jordan will help. A formal referral letter must be sent to the appropriate person and the clinical nurse specialists need to be informed. Patients will usually be admitted to RBH prior to surgery.

When necessary, patients will be admitted to RBH least 48 hours prior to surgery to commence intravenous antibiotics. Physiotherapy should also be intensified for at least 24 hours before surgery. However if IV access is a big issue, then we may need to wait until the Portacath is sited before starting IVABs.

Post insertion

- Chest x-ray for line position and pneumothorax.
- Analgesia - Regular Paracetamol 500mg – 1G QDS +/- Ibuprofen 200-400mg TDS or Diclofenac 50mg TDS or Oramorph 2.5-5mg Q4H. A laxative should be given at the same time if necessary.
- Physiotherapy and early mobilisation are important.
- Antibiotics continued for a minimum of 48 hours post-procedure, and until patient is pain free and back to usual respiratory status.
- Portacath may be used from the time of insertion and the needle should be left in by the surgeons.
- Sometimes dissolvable sutures are used – but it is important to check before the patient goes home.
- There is some evidence that using the port to take blood samples increases the risk of line infection. Therefore bloods should only be taken after consultation with one of the clinical nurse specialists.

Subsequent management

4-6 weekly flushing with 3ml 0.9% sodium chloride followed by 4mls of heparinised saline (ready made as 200 units per 2 mls). This is arranged through the CF nurse specialist with the home care team, in the hospital or local community nurses. Relatives/partners can also be assessed if they wish. Local anaesthetic cream can be used if necessary.

- Always use the proper needle (straight bevelled – ‘Huber’).
- Always use a sterile technique.
- The port is not to be touched by the inexperienced, particularly inexperienced doctors.
- After flushing, clamp the line (using clamp nearest the needle) then remove needle.

Complications

- **Blockage** - consider Urokinase 5,000 units in 3ml 0.9% saline instilled into port. Leave for 2-4 hours then aspirate and flush gently with 3ml 0.9% sodium chloride followed by 3ml heparinised saline (10units/ml). Use with caution if there is a history of bleeding or significant haemoptysis.
- **Port leak** - may occur if a forceful flush is attempted when the line is blocked or if the wrong type of needle is repeatedly used damaging the diaphragm. Diagnosis is with a contrast portagram.
- **Local infection** - around the port - clean area, if device is visible then it needs removing but if the inflammation is superficial then treat with systemic antibiotics after swabs and blood cultures have been taken. Antibiotics should be administered via another line.
- **Line infection** - usually demands surgical removal. After cultures have been taken, systemic antibiotics via another route and possibly injecting vancomycin or teicoplanin into the system may work. Thrombus may form which may lead to septic pulmonary emboli. Blood cultures and an echocardiogram may help the diagnosis and sometimes radio-opaque contrast can collect in a thrombus if injected down the line. Beware of injecting into a line that may have thrombus around it - you may cause pulmonary embolism, so think first and be careful. Consider anti-coagulation.
- **Catheter fracture ± embolisation** - fragments should be retrieved at cardiac catheterisation. Refer immediately to interventional radiologist (Dr Simon Padley).
- **Tinnitus** – at the time of antibiotic administration may indicate line migration into the neck veins passing cranially. A portagram should be arranged and findings discussed with interventional radiologist (Dr Simon Padley).

3.6 SPECIALIST PHYSIOTHERAPY TEAM

Outpatients

A specialist physiotherapist is available in clinic to assess all patients and discuss/review physiotherapy management. There are a large variety of airway clearance techniques (ACT) available to patients. Which technique is selected will be discussed with each patient and will be based upon their disease presentation, lifestyle and individual needs.

The regime of airway clearance (including frequency and duration) advised for each patient will vary depending on infective exacerbations, severity of disease and individual circumstances.

Airway clearance techniques available include:

- **The Active Cycle of Breathing Techniques (ACBT)** – a combination of thoracic expansion exercise, breathing control and the forced expiration technique.
- **Autogenic Drainage** – A phasic breathing regime utilising high expiratory flow rates at variable lung volumes.
- **Positive Expiratory Pressure (PEP)** – provides resistance to expiration through a mouthpiece or face mask. Can be used in conjunction with breathing exercises.
- **Flutter** – Pipe shaped device that creates oscillations and positive pressure on expiration. Can be used in conjunction with ACBT.
- **Acapella Choice** – Green device with a mouthpiece that provides oscillation and positive pressure on expiration. Can be used in conjunction with ACBT.
- **HFCWO (the VEST)** – A vibrating jacket that can be worn during airway clearance to provide oscillations to the chest wall. Recommended to be used in conjunction with airway clearance techniques.

- **Positive pressure** – Either in the form of the IPPB (BIRD) device as an inpatient or using a non-invasive ventilator in the home setting, positive pressure can help improve thoracic expansion, and decrease work of breathing with airway clearance.

***Cleaning and disinfecting the airway clearance device is vitally important
(refer to manufacturers' guidelines)**

Other physiotherapy issues that may be discussed are:

- **Exercise** – The importance of exercise is regularly highlighted in clinic and at annual review. Exercise regimes are prescribed for inpatients following discussion with each individual patient. Exercise testing is carried out when needs are identified, a variety of tests are used.
- **Posture** - The possibility of postural adaptations or musculoskeletal discomfort will be assessed and discussed with patients at annual review and during inpatient stays. Musculoskeletal treatments and exercise regimes can be accessed through the CF physiotherapy team or through onward referrals to local services.
- **Stress Incontinence** – This is prevalent in adolescents and adults with CF during activities such as exercise, ACT and laughing. Most symptoms can be easily managed with pelvic floor re-training. Screening for symptoms of stress incontinence will occur at annual review, and as inpatients. Advice on treatment strategies can be obtained from the CF physiotherapy team with possible onward referral.
- **Inhalation therapy** – Devices and medications available for nebulisation are frequently evolving. It is recommended that patients discuss their needs with their specialist physiotherapist who can advise them on the most suitable regime.

Inpatients

All patients admitted to RBH will be assessed and physiotherapy requirements established within 24 hours of admission. Physiotherapy assessments and interventions will be carried out in the individual patients' room. If necessary, airway clearance regimes will be modified, and patients may require additional intervention and equipment during exacerbations. A weekend service is available for appropriate patients. On discharge a plan for home regimes will be created with the patient. Referral to the homecare physiotherapy service will be made is deemed necessary.

3.6.1 Physiotherapy advice regarding inhalational therapy

Inhaled medication should be coordinated with physiotherapy:

- **RhDNase** – Needs dwell time within the lungs after nebulisation to be effective. A minimum of 30 minutes to 1 hour is advised prior to treatment; however alternative regimes are possible and should be discussed with a specialist physiotherapist. It is not advisable for patients to nebulise RhDNase just prior to going to bed in adults.
- **Bronchodilators** – long acting bronchodilators (e.g ipatropium) should be taken at least 45 minutes prior to airway clearance, short acting bronchodilators (e.g. salbutamol) should be taken 10 minutes beforehand. Spacers are advised to be used where possible to improve deposition.
- **Hypertonic saline 7%** – Should be taken prior to commencing airway clearance, following a bronchodilator (if prescribed).
- **Steroid inhalers** – Advised to be taken after airway clearance if possible.
- **Nebulised Antibiotics** – Should be taken after airway clearance.

For inhaled antibiotics and hypertonic saline the patient must always be assessed for

bronchoconstriction when the 1st dose is given. This should be done at the hospital and requires the patient to perform pre and post dose spirometry. The following equation is useful to work out % constricted (> 15% is significant): $(\text{Pre-dose FEV}_1 - \text{post-dose FEV}_1) \div \text{Pre-dose FEV}_1 = \% \text{ bronchoconstriction}$

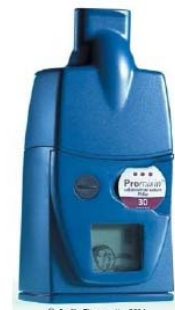
If the patient cannot perform spirometry then they are observed having their first dose and chest auscultation is performed. Oxygen saturations (SpO₂) are monitored throughout the test.

Nebulisation Devices

RBH provides nebulisation devices to patients who require nebulised medications. These systems include conventional air compressors and alternative devices such as the I-NEB and E-Flow. Devices vary in suitability for patients depending on situation and drugs prescribed. Each patient will be assessed on an individual basis.

Philips Respironics I-neb®

This is a breath actuated device and only emits aerosol on inspiration. It has superseded the Halolite and Prodose as the 3rd generation Adaptive aerosol delivery device (AAD). The I-neb® incorporates a piezoelectric element that vibrates a transducer horn which pulses fluid through a mesh consisting of thousands of tapered holes which reduces inhalation time.



Pros	Cons
<ul style="list-style-type: none"> - Fast nebulisation: Promixin® (colistin) and rhDNase 1min - Virtually silent - Lightweight/portable - Battery or multi-volt power - Breath activated (inhalation only) AAD® - No filtering of antibiotics required - 2 breathing modes – Tidal Breathing (TBM) and Target Inhalation (TIM) - TIM can speed delivery and improve lung deposition (as long as FEV1>1L) - Device, maintenance and replacement parts free - 1 MU Colistin in I-neb® delivers equivalent of 2MU via conventional nebuliser - Can download usage data to review compliance and trouble shoot if nebulisation time increasing 	<ul style="list-style-type: none"> - Can only be used if can inhale through mouthpiece (>2 years) - Only currently available if on Promixin® - Cleaning time consuming, components delicate - Holes in mesh can block increasing treatment time - Poor breathing technique can increase treatment time - Can only nebulise Promixin®, rhDNase, Salbutamol, TOBI® and hypertonic saline - TOBI® and hypertonic saline must be nebulised twice in larger lilac chamber to give 1ml dose to lung - Can't nebulise Bramitob through the I-neb® - Some medications may taste stronger

This table can be used when switching nebulised colistin from a conventional compressor to the I-NEB.

Colistin Dose	Conventional Compressor	I-neb® - Promixin®
2 MU	2MU	1MU (mix with 1ml saline)

Tobramycin 300mg/5mls and hypertonic saline 7% 4mls can be nebulised through the I-Neb. The table below may be useful for working out doses and fill volume.

Device	Drug	I-neb Chamber	Fill Volume	Number of nebulisations
Conventional Nebuliser	Tobi [®] 300mg/5mL	N/A	5mL	1
I-neb AAD	Tobi [®] 300mg/5ml	0.5mL (use lilac latched component) *	2.5mL	2
Conventional Nebuliser	Hypertonic Saline 7%/4mL	N/A	4mL	1
I-neb AAD	Hypertonic Saline 7%/4mL	0.5mL (use lilac latched component)	2mL	2

* This is a lilac coloured flap that covers the disc containing the drug when giving TOBI



PARI eFlow[®] rapid

The PARI eFlow[®] rapid uses touch spray vibrating mesh technology and reduces inhalation time by 50% compared to the Pari LC Plus[®]. Cleaning and disinfection of the nebuliser device is vitally important (follow manufacturer's advice).

PARI eFlow [®] rapid - Pros	PARI eFlow [®] rapid - Cons
<ul style="list-style-type: none"> Fast nebulisation time: TOBI 6-8 mins, Colomycin 3-4 mins, HTS and DNase 2-3 mins A larger variety of drugs can be used with this system compared to the I-Neb Virtually silent and light weight Battery or multi-volt power Can be used with all ages (mask or ideally mouth piece) 	<ul style="list-style-type: none"> Not 'breath-activated' Continuous flow, so some drug is wasted in expiration and filtering is required for antibiotics Medications may taste stronger Cleaning time consuming compared to air compressor systems Holes in mesh can block increasing treatment times, especially if not optimally cleaned Poor breathing technique can increase treatment time

3.6.2 Oxygen therapy

Supplementary oxygen is provided to those patients who fit the criteria outlined in the oxygen policy for RBH (see trust intranet). Oxygen assessments will be carried out in the inpatient and outpatient setting as required.

The oxygen technician (ext 4453 or bleep 7755) is available to help with oxygen orders, exercise testing and general queries.

3.6.3 Non-Invasive Ventilation

Non-invasive ventilation is helpful for those patients with advanced disease, especially those with carbon dioxide retention, increased work of breathing, or difficulties with oxygenation. Non-invasive ventilation can

be used overnight or during the day for rest or activity, for example it can be helpful when combined with physiotherapy techniques for sputum mobilisation and exercise to increase functional capacity. The set up of non-invasive ventilation is carried out with careful assessments, which may include arterial blood gases and overnight sleep studies, alongside discussions with the patient and the CF team. Each patient will be assessed for suitability for non-invasive ventilation on an individual basis.

3.7 SPECIALIST DIETETIC SERVICE

Outpatient Clinic

- All adult cystic fibrosis patients have their weight checked at each clinic appointment. Patients aged ≤ 19 years of age or who haven't yet reached skeletal maturity will also have their height measured at each clinic appointment.
- The specialist dietitian will aim to review the nutritional and gastrointestinal state of every patient at each clinic attendance particularly if there are concerns impacting on nutritional status and/or weight.
- Assessment of dietary intake including the use of dietary supplements and enteral tube feeds is carried out by the cystic fibrosis dietitian along with pancreatic enzyme replacement therapy, glycaemic control and vitamin supplementation; which are reviewed as appropriate.

Transition to Adult CF Outpatient Clinic

The specialist dietitian will attend transition clinic appointments alongside the paediatric cystic fibrosis dietitian. This provides patients' with the opportunity to meet the adult dietitian and ask any questions they may have regarding adult cystic fibrosis services. It also enables the beginnings of a rapport to be built and allows the adult dietitian to explore if there are any aspects of a patient's care that may require more attention to detail.

Annual Review

All patients will have a one to one consultation with the cystic fibrosis dietitian at their annual review. This will involve a detailed nutritional assessment with a written report involving all aspects of cystic fibrosis care that impact on nutritional status.

Outreach Service

A dietetic outreach service via telephone or email is available for adult CF patients who have a need for close dietetic attention whilst at home. For example; support for patients who have recently been discharged home from hospital with a new gastrostomy placement or recently been diagnosed with cystic fibrosis related diabetes. Patients are provided with dietetic contact details during outpatient appointments and hospital admissions so dietetic support at home is available if required.

Admission to hospital

A blanket cover system is in place so all adult cystic fibrosis patients are nutritionally assessed by a cystic fibrosis dietitian during every hospital admission. Nutritional needs of patients are met through the provision of additional snacks and high calorie meals. Oral nutritional supplements, enteral tube feeding or parenteral nutrition can also be provided as necessary. Review and advice regarding pancreatic enzyme therapy, vitamin supplementation and diabetes care is undertaken as clinically indicated.

3.8 SPECIALIST PHARMACY SERVICE

The pharmacist is an active member of the multidisciplinary team and the specialist pharmacists attend the weekly multidisciplinary cystic fibrosis ward round, and actively contribute to patients care by assisting the team with making clinical decisions regarding treatments.

Inpatient Service

All patients with cystic fibrosis who are admitted to hospital will be assessed by the pharmacy team on admission: within 24 – 48 hours of admission, a member of the pharmacy team will undertake medicines reconciliation. Self-administration is encouraged, therefore patients' own medications are assessed for suitability to use during their inpatient stay, and additional medications are supplied as required. Medication lockers are available in each room and must be used. The pharmacist will visit the ward twice daily in the morning and afternoon Monday - Friday and are available between 9 – 5.30 to discuss all aspects of medication with both patients and the CF team. During the ward visits the pharmacist will see each patient and review their medication chart to ensure that patients are prescribed the correct, safe and appropriate medication. Where appropriate the pharmacist will discuss the patient's treatment plan with them, answer any questions regarding their medicines, and counsel patients about their medicines where needed to aid adherence. Any medication related issues such as an inappropriate dose or choice, side effects, allergy, or supply problems will be discussed with the doctors and resolved, and any medicines where blood levels need to be monitored will be checked by the pharmacist. Outside normal working hours, an on-call pharmacist is available for advice.

On discharge, each patient is given an up-to-date list of their medication which has been checked by a pharmacist. All changes to therapy are highlighted to patients' GP's to ensure that all necessary medications are continued.

Outpatient dispensing

Prescriptions written in clinic and prescriptions for IV antibiotics to cover until homecare delivery are dispensed by an outpatient dispensary. There is always a pharmacist available for prescribing advice for prescribers in clinic (in addition to the specialist pharmacists) and patients receive medication counselling and advice on prescription charges and pre-payment certificates where appropriate.

Annual Review

All patients will have a one to one consultation with a cystic fibrosis pharmacist at their annual review. This will involve a detailed medication history, adherence review, review of supply arrangements and education.

Homecare

The specialist pharmacy team are responsible for ensuring patients have access to the medicines they need. Most medicines will be supplied after discharge by general practitioners (GPs), however, arrangements are in place for home delivery of certain medications to patients via a third party homecare company. This service is extended to all patients who are prescribed Tobi Podhaler®, aztreonam lysine (AZLI/Cayston®), mannitol (Bronchitol®) and ivacaftor (Kalydeco®), which are not routinely prescribed by GP's. If a patient does not wish to have their medication supplied in this way, they must make arrangements to collect these medicines from RBH.

All other patients may be registered with the service for certain other drugs if their GP is unable to prescribe them (for example, Pulmozyme®, colomycin, Tobi® and Bramitob®, and other inhaled medicines such as meropenem, amikacin and ceftazidime). The pharmacy team complete registration, supply prescriptions and

liaise with homecare companies regarding delivery of medication and problem solve for individual patients as required.

Medicines Helpline

A medicines information service is available via telephone or email to all adult CF patients who have a need for further information about their medicines while they are at home. This may include information about newly prescribed medicines, problems with the supply of medicines from GP or community pharmacy, or to check for interactions between currently prescribed medicines and any new conventional or herbal medication which the patient wishes to use.

The medicines information team is led by a specialist medicines information pharmacist who works closely with the specialist CF pharmacists and will discuss medicines related questions for specific patients. Healthcare professionals may contact medicines information directly, however, we recommend that a specialist CF pharmacist is contacted in the first instance.

Email: medinfo@rbht.nhs.uk Tel: 0207 351 8901

3.8 CLINICAL PSYCHOLOGY

The clinical psychology team attend the Wednesday am MDT ward round to discuss referrals and to feedback to the consultants. They provide a service to both inpatients and outpatients. Outpatient psychology appointments are coordinated with the routine CF clinic appointments.

The clinical psychologists recognise that CF can affect young and older adults in a variety of ways. We offer the opportunity to discuss any fears, anxieties or problems that can arise from living with CF and the burden of treatment. As well as talking and listening, the psychologists offer help to find ways of coping with difficult situations.

Some of the reasons for referral or consultation include:

- Coping with a new diagnosis of CF
- Informing friends and family about CF diagnosis and managing their reactions to this
- Helping a person with CF to manage their treatments
- Managing invasive procedures including fear of needles
- Helping a person with CF to cope with nutritional management eg: considering gastrostomy feeding
- Work problems
- Managing a family
- Considering transplantation
- Issues towards the end of life

4: ADMISSION TO HOSPITAL

4.1 ARRANGING AN ADMISSION

There are several reasons why an adult with CF requires an admission to hospital. The commonest is a requirement for IV therapy in the context of an exacerbation. Other reasons include haemoptysis, pneumothorax or DIOS. Finally an adult patient with newly diagnosed CF may require admission for assessment and treatment. Patients are also admitted electively prior to procedures such as gastrostomy insertion etc.

The request for admission is documented via the nurse specialists and the Anglia Ice form is completed. The admission list is discussed daily with the ward consultant to ensure prioritisation of available beds. Anyone requesting an admission should ensure good documentation of the patient history so that each patient can be categorised as either a) requiring urgent admission within next 48 hours or b) admission required within 7 days or c) non urgent admission ie: elective with planned date.

Cross infection issues are a priority, therefore patients with CF are only admitted to Foulis ward into single, ensuite rooms. The ward nursing staff are skilled at CF care, including long lines insertion, aminoglycoside levels, nursing patients on NIV and palliative care. The ward nurses work closely with the CF MDT and with the patients to agree a complete package of care at each admission.

4.2 ASSESSMENTS & INVESTIGATIONS

The CF integrated care pathway documentation should be completed. The reason for hospital attendance must be identified and the medical clerking should be followed according to the ICP.

- The most recent sputum culture results should be documented.
- The patient's most recent and best (within the last year) pulmonary function tests (FEV1, FVC) must be recorded
- Past history of ABPA (if applicable) should be recorded with most recent IgE & Aspergillus RASTs, together with maximum values in the past year for comparison.
- A full drug history including the types of inhaler used (e.g. turbohaler, MDI with spacer etc) is mandatory. Inhaler technique must always be checked. Drug doses are often recorded in the last clinic letter but **do not** rely on these. All drug doses should be checked directly with the patient before recording and prescribing them. If a patient is on oral steroids, record the starting date and dose. Check whether there have been problems with aminoglycoside levels in the past. Any allergies, particularly to drugs should be recorded both in the notes and on the drug chart, the type of reaction experienced should also be included (e.g. rash, anaphylaxis).
- Nebulised antibiotics can be discontinued if the patient is receiving intravenous antibiotics but these must be reinstated on discharge.
- Any with-held medicines should be recorded on the front of the medication chart
- Drug histories and medication charts are checked by the pharmacy team at the earliest opportunity.
- A full social history should be taken paying particular attention to the situation regarding school, college, university or work, housing issues and alcohol and nicotine use.
- Spirometry must be performed within 24 hours of admission.
- A chest X-ray is performed on admission

- The list of admission bloods is as follows:

Haematology	Full blood count (FBC) Urea & electrolytes Liver function tests
Biochemistry	Calcium, magnesium, phosphate Glucose HbA1C Aspergillus RAST CRP
Virology/Immunology	Aspergillus IgG

4.3 IV ACCESS

Many adults will have had previous experience of intravenous antibiotics and will have a preferred method of IV access, this should be respected. The choices offered are: peripheral cannula (venflon), long-line or Portacath. Some patients may require PICC lines which are organised via radiology.

4.4 INFECTION CONTROL

- Each adult with CF is admitted to a single room with ensuite facilities.
- No adult with CF should enter another CF adult's room.
- Waiting around in corridors is discouraged.
- No CF adult should sit or wait around the nurses station including during the evening and at night
- Disinfectant hand rub dispensers are outside each cubicle for use by staff, families and visitors
- Adults are asked to sign the patient contract to ensure they understand the rules regarding cross infection

4.5 BEING AN INPATIENT

Daily Plan

The CF team doctors will assess patients on a daily basis. Additionally, each patient room has a whiteboard within it which can be used to create a daily plan of their hospital stay. This process involves the multidisciplinary team using the whiteboard to timetable in appointments, investigations and treatments in discussion with each individual patient. The school teachers can also book in time, exams, art etc and the reflexologist and singing teacher can book appointments.

4.6 DISCHARGE

On discharge the adult with CF should receive information regarding their next outpatient appointment and a full explanation of the drug regimen for use at home. If the patient is continuing on IV therapy at home they may require follow up at home with the nurse specialists via telephone clinic or visit. This will be agreed by the MDT.

5: DIAGNOSIS

5.1 CLINICAL PRESENTATION

Confirming the diagnosis of CF requires a clinical picture consistent with the CF phenotype and laboratory evidence of CFTR dysfunction. In the majority of cases the diagnosis is straightforward; clinical suspicion should be raised if one or more of the following is present:

- (1) Chronic sinopulmonary disease such as bronchiectasis (\pm finger clubbing), nasal polyposis, persistent airways infection with *Staphylococcus aureus*, *Pseudomonas aeruginosa* or *Burkholderia cepacia* complex.
- (2) Gastrointestinal manifestations such as malabsorption, pancreatic insufficiency, recurrent pancreatitis, distal intestinal obstruction syndrome or focal biliary cirrhosis.
- (3) Male infertility due to CBAVD and obstructive azoospermia.

As CF disease expression is highly variable, diagnosis in adulthood does occur and may be more challenging, especially if BMI is normal (up to 10% of patients are pancreatic sufficient). Such patients often have a borderline sweat test and their disease is usually termed 'atypical' or 'non-classic' CF. A new diagnostic entity – CFTR-related disorder – has also recently been introduced (which encompasses atypical CF) and is defined as "a clinical entity associated with CFTR dysfunction that does not fulfill diagnostic criteria for CF." Clinical presentation after the neonatal period will become rarer with time as neonatal screening is now performed in the UK. However, it is essential that the diagnosis is not ignored or 'ruled out' if a young adult was born while screening was being introduced as screen failures do occur.

Sweat testing and genotyping are the most common methods used to confirm evidence of CFTR dysfunction, but in equivocal cases, measurement of transepithelial nasal potential difference are indicated. See Figure for the diagnostic algorithm.

5.2 INVESTIGATIONS

5.2.1 Sweat Test

Sweat testing will make the diagnosis in up to 98% of patients but is much less reliable in patients with atypical disease manifestations.

Sweat is stimulated by pilocarpine iontophoresis. We perform the sweat test using the macroduct system, as opposed to the older Gibson & Cook methods, with which evaporation (leading to falsely elevated sweat electrolyte levels) was a problem. Therefore, 100mg of sweat is no longer required, and analysis can be reliably performed on smaller quantities. Minimum of 20 minutes and maximum of 30 minutes is the recommended testing time.

As with any of these techniques, it is extremely important that they are performed by personnel who are experienced. Only the CF nurse specialists carry out our sweat tests. The sweat is analysed by the Biochemistry lab and results include sweat volume and Cl^- levels. National guidelines for sweat testing have been finalised and are available on www.acb.org.uk/.

Results must be interpreted in the clinical context

Normal range: $\text{Cl}^- < 30 \text{ mmol/l}$
Equivocal range: $\text{Cl}^- 30 \text{ to } 60 \text{ mmol/l}$.
CF confirmed: $\text{Cl}^- > 60 \text{ mmol/l}$.

Data from Australia led to a decrease in the cut-off for 'normal' values in screened infants from 40 to 30 mmol, as the latter is four standard deviations above the mean (Farrell PM et al. Pediatrics. 1996;97:524–8). It is also recognised that some genotypes are associated with a low or normal sweat chloride, such as the mutation 3849+10kbC>T. Chloride is the primary ion measured; sodium should not be measured alone. We do not measure conductivity and do not advocate its use. In normal health, sweat Na^+ is usually higher than Cl^- . This ratio is sometimes reversed in CF. This may be helpful, but is certainly not diagnostic. The diagnosis of CF should be made on the basis of two sweat test results not one - we take two samples at the same time. If there is any doubt over a result, repeat the test or discuss it with a consultant. Flucloxacillin has no effect on a sweat test result.

False negative results. Cases are recognised where the clinical picture of CF is supported by genotyping, but in the presence of a normal sweat test (<1% CF patients). Beware therefore of excluding the diagnosis (in highly suggestive cases) on the basis of a normal sweat test alone. Genetic testing, and possibly nasal potential difference testing, should be performed. Please discuss with Dr Nick Simmonds or Dr Jane Davies.

False positive results. Many theoretical causes as listed in textbooks, most of which do not appear to cause problems in routine clinical practice. Those which may be encountered include malnutrition or skin disorders such as severe dermatitis/eczema. Transient increases in sweat electrolytes have also been reported in young patients with immunodeficiency states.

5.2.2 Genetic Analysis

At least 1900 mutations in the *CFTR* gene have been reported, of which at least 160 are known to be definitely disease causing. Mutations fall into different classes (I-VI), with the commonest in Caucasian populations being a class II mutation, F508del. Nomenclature has changed recently (see appendix XI).

Indications for genotyping include the following:

- As part of the diagnostic work-up (unless clinical index of suspicion low and sweat chloride <30 mmol/l).
- Screening of other family members (although generally siblings will have a sweat test rather than genetic analysis). Note that carrier testing is **not** carried out in siblings until they are old enough to decide whether they wish it done (mid teens).
- Screening of the patient's partner if they are considering starting a family.

Screening of family members and partners should be performed at the local genetics centre, not RBH, to ensure comprehensive genetic counselling takes place.

With the advent of mutation-specific therapies, all CF patients should be genotyped (extensively, if necessary) to allow inclusion into clinical trials and, possibly, to direct future treatment.

Based on current knowledge, genotype analysis should not be used to guide prognosis in an individual patient, except rarely (and cautiously) in the case of mutations usually associated with pancreatic sufficiency (e.g. R117H). Pancreatic status should be confirmed with a faecal elastase in all cases. Although studies have shown a milder lung phenotype in certain groups such as these, patients with typical, severe lung disease have also been described, hence it is best not to prognosticate in individual cases. There can also be problems

occasionally with a genetic diagnosis of CF in a patient who is asymptomatic with no apparent CF phenotype. These must be discussed with the consultant.

Limitations of mutation analysis

Routine *CFTR* genotyping uses techniques that detect mutations that are common to the specific population of the country or region that it serves. For example, most laboratories in the UK genotype for 50 mutations, detecting 85–90% of alleles in white Britons.³⁴ Consequently, two mutations will not be identified in a significant proportion of affected individuals (approximately 25%), especially if they are non-white. For this reason it is important that in every case the patient's ethnic origin is included on the request form. If two mutations have not been identified, extended genetic analysis can be performed by multiple exon DNA sequencing and multiple ligation-dependent probe amplification (MLPA). This is a highly sensitive test (approximately 98%), but on rare occasions it will fail to identify a mutation. Fundamentally, CF remains a clinical diagnosis supported by evidence of abnormal *CFTR* function; genotyping should be regarded as supportive as, currently, it cannot always provide definitive evidence. Extended genotyping can be performed if specifically requested but is expensive (in the order of £500) and time-consuming and therefore not done routinely. Routine samples should be sent to the Kennedy Galton Centre (Northwick Park Regional Genetics Centre).

Practicalities of genetic testing

Take blood (10ml) into EDTA bottle.

Complete genetics form on the RBH intranet.

Samples need to be sent to the Clinical Biochemistry Laboratory who will forward them to KGC.

KGC will perform extended analysis if specifically requested (and 1st line testing was negative).

5.2.3 Nasal Potential Difference Measurement

Nasal potential difference (PD) measurement takes advantage of the two main components of *CFTR*-mediated ion transport in the respiratory tract: Cl^- secretion and Na^+ absorption. In CF, the lack of functional *CFTR* in the apical membrane results in defective Cl^- secretion, coupled with Na^+ hyperabsorption. Nasal PD measures the voltage created by Cl^- and Na^+ as they shift across the epithelium. Although not yet fully standardized, its utility in the diagnosis of difficult or possible CF cases is generally well recognized and it is an integral component of the European diagnostic CF algorithm (De Boeck et al. Thorax 2006; 61:627-35).

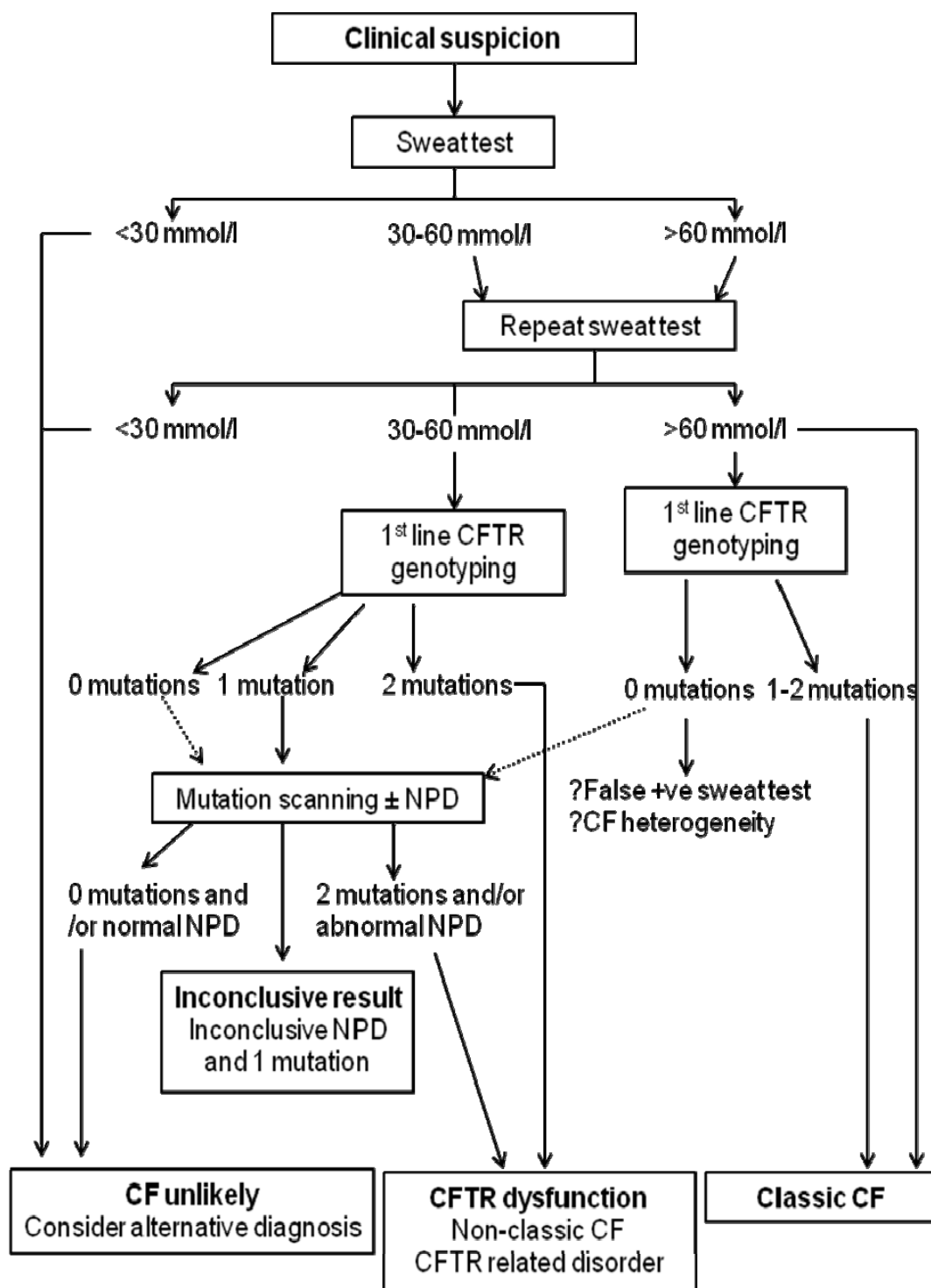
5.2.4 Other Tests

These may be supportive of the diagnosis:

- **Stool elastase:** low in CF with pancreatic insufficiency (usually <15 mcg/g).

Normal	> 200 mcg/g stool
Mild/moderate pancreatic insufficiency	100-200 mcg/g stool
Severe pancreatic insufficiency	< 100 mcg/g stool
- **Fludrocortisone suppression test.** In grey cases with repeat sweat levels in the equivocal range this test may help differentiate CF from normal, although with nasal PD and extended genotyping, it is now largely a redundant test.

Diagnostic algorithm



6: RESPIRATORY CARE AND MAINTENANCE

Information on drugs mentioned in this section can be found in the CF Formulary in the Appendix

6.1 INFECTIONS

Aggressive treatment of pulmonary bacterial infection with antibiotics is the most important and effective intervention in the treatment of CF.

The aim of treatment is to reduce the burden of infection in the airways. The commonest bacteria that infect the airways in CF are *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA).

Other bacteria that can infect some patients in adulthood include *Achromobacter xylosoxidans*, *Burkholderia cepacia* complex and *Stenotrophomonas maltophilia*. Non tuberculous mycobacteria (NTM) are recognised as troublesome infections. We have written a separate guideline for treatment of NTM (see RBH guideline: Guidelines for the treatment of non-tuberculosis mycobacteria in patients with cystic fibrosis, available on the RBHT intranet <http://www2.rbht.nhs.uk/search/?q=non-tuberculosis+mycobacteria>).

Treatment of infections depends on regular surveillance of respiratory samples. A sputum sample is obtained at every clinic visit or clinical encounter. If sputum is not available a cough swab is obtained. If a patient has evidence of clinical deterioration in the presence of negative cough swabs then more invasive sampling should be pursued, first with induced sputum via hypertonic saline followed by bronchoscopy if unsuccessful.

6.1.1 Eradication

***Staphylococcus aureus* positive surveillance cultures**

- If the adult is already on flucloxacillin prophylaxis and is clinically well with stable lung function and no new symptoms extra treatment may not be required. However, if the patient is less well an increased dose of flucloxacillin can be given or an alternative anti-staphylococcal agent.
- If the patient has a first isolate of SA and is not already on flucloxacillin then this will normally be treated regardless of symptoms with flucloxacillin 1 gm bd for 2 weeks to a month.

***Pseudomonas aeruginosa* positive culture**

- A first isolate of PA or a new isolate following previous eradication should always be treated.
- If the adult is stable with unchanged lung function and no new symptoms start eradication therapy with oral ciprofloxacin and nebulised colistin. The ciprofloxacin is continued for 1 month and the colistin is continued for 3 months. (however, latest data suggests that TOBI for 1 month could replace colistin)
- If the patient is less well then intravenous antibiotics should be administered followed by nebulised anti-pseudomonal therapy.
- If eradication is successful and then there is a subsequent new isolate further eradication can be attempted. Some patients will have successful eradication on 3 occasions over 6 – 9 years before becoming chronically infected.
- If eradication with nebulised therapy is unsuccessful then the adult should receive a course of IV antibiotics as a further eradication attempt before accepting chronic infection.

***Achromobacter xylosoxidans* and *Burkholderia cepacia* complex**

There is little data regarding successful eradication treatment for these organisms. However, as they are associated with an excess morbidity and for *B. cenocepacia* mortality we believe it is worth attempting eradication in response to the first isolate.

MRSA

There is good data to show that MRSA confers worsening lung function and so it is well worth attempting eradication. If the patient is stable then we recommend eradication with oral antibiotics using a combination of rifampicin and fucidic acid. In the event of deteriorating lung function and new symptoms we would recommend treatment with intravenous vancomycin.

Oral or IV eradication therapy should be accompanied by appropriate topical eradication therapy.

Stenotrophomonas maltophilia

These bacteria can emerge after successful treatment of PA. It may not require treatment but in some patients it is associated with new symptoms and changes in lung function. Oral cotrimoxazole can be very effective in this situation.

6.1.2 Chronic suppressive therapy

Patients who have become chronically infected with PA should be established on long term inhaled or nebulised anti-pseudomonal antibiotic therapy. This treatment approach is known to preserve lung function and reduce exacerbations. Our treatment approach is as per the national specialist commissioning policy for CF medicines. First line - nebulised colistin twice daily. In the event of deteriorating lung function and/or requirement more than one IV course per year we add in nebulised TOBI or Bramitob or inhaled dry powder tobramycin on alternate months.

If a patient is deteriorating despite alternating TOBI, colomycin then nebulised aztreonam lysine can be substituted.

Patients chronically infected with other gram negative bacteria such as *Achromobacter* or one of the *Burkholderia cepacia* complex should be established on long term nebulised antibiotic therapy targeted against the particular bacteria. For *Achromobacter* this will usually be colistin as first line. As the *B. cepacia* complex bacteria are uniformly resistant to colistin the choice will be between nebulised ceftazidime, meropenem, TOBI or aztreonam lysine.

For *A. xylosoxidans*, first line we use a licensed nebulised antipseudomonal agent if the patient's culture is sensitive. Our second line agent is nebulised meropenem. For *B. cepacia*, we use a licensed nebulised antipseudomonal agent first line if the culture is sensitive. Second and third line agents are nebulised meropenem, ceftazidime and temocillin. (See also RBH Guideline: Antimicrobial Prescribing Guide, available on the Intranet)

6.2 TREATING EXACERBATIONS

If the patient is worried they will usually phone the CF nurse specialists or the ward registrar. Advice can be given for home treatment, day case review or clinic visit, however the patient may need to be admitted. Records of telephone advice must be recorded on EPR. Indications of chest exacerbation include:

- Changes in sputum production (volume, colour, consistency).
- Haemoptysis.

- Increased cough.
- Increased dyspnoea.
- Chest pain or tightness.
- Malaise, fatigue and lethargy.
- Fever (note that most CF chest exacerbations are **not** accompanied by fever).
- Loss of appetite or weight loss.
- Drop in FEV₁ from previous recording.
- Adverse changes in chest sounds on auscultation (crackles, wheeze). However a clear chest on auscultation does **not** exclude an infective exacerbation.

If the situation is dealt with over the telephone, it is essential that the CF nurse specialist is informed, so appropriate follow up (outreach team, telephone) can be arranged. It is important that sputum or a cough swab is sent to microbiology. A chest x-ray or bloods do not have to be performed at every infection. Antibiotics should be prescribed, initially orally +/- inhaled or nebulised, with IV antibiotics given if the patient fails to respond. Repeated oral courses are useful to cover viral infections, however multiple oral courses when the patient is not responding are not useful.

6.2.1 Antibiotic choice for intravenous therapy

There is no evidence that in vitro sensitivities correlate with in vivo outcome for treatment of an exacerbation of PA infection. It is therefore important to simply follow the antimicrobial prescribing guide for CF. First line therapy is with ceftazidime and tobramycin with second line being meropenem and tobramycin. Always discuss any variations with this with consultant.

6.2.2 Aminoglycoside levels

Tobramycin is the aminoglycoside of choice for treating PA infection. Tobramycin is administered once daily and trough levels are measured as per the antimicrobial prescribing guide. Amikacin is only used in treatment of NTM. Gentamicin is not used.

6.3 IMPROVING SPUTUM CLEARANCE

6.3.1 RhDNase (Pulmozyme)

Pulmozyme is a synthetic enzyme that cleaves neutrophil derived DNA in sputum to reduce viscosity and thus in theory to aid sputum removal. Studies demonstrate 5-8% overall improvement in FEV₁, and reduced exacerbations. Recently it has been shown to be associated with increased survival.

Indications:

If an adult is not already on Pulmozyme consider starting if spirometry is less than 85% or, even in the presence of normal FEV₁, if there is decline in small airways function.

Dose:

2.5mg nebulised daily. Some teenagers are transferred from paediatrics using this on alternate days. This may be acceptable if lung function is stable and there are very infrequent exacerbations. However, daily therapy is recommended if there is evidence of deterioration.

Judgement of response:

A trial should be 3 months long especially for the most severely affected ($FEV_1 < 40\%$). There is a good correlation between response at 3 months and that seen after 12 months treatment.

Side effects:

Rare and mild; hoarse voice occasionally and rash sometimes seen. There is no need to stop use in patients with haemoptysis or pneumothorax

6.3.2 Hypertonic saline (7%)

HTS can cause bronchoconstriction, so pre-treatment with a bronchodilator should always be given. The first dose should always be given with spirometry before and afterwards (this is booked with the physiotherapists). In all cases, HTS is given immediately before physiotherapy. If HTS cannot be tolerated, lower concentrations may be considered. We use Nebusal (7% hypertonic saline) that comes in individual 4ml single dose plastic ampoules and is prescribable by GPs.

- For sputum induction, which may be indicated in the CF patient who is not doing well, but does not expectorate sputum spontaneously, we use 3.5% saline ('normal saline-0.9%). To achieve this concentration dilute 2 ml 7% hypertonic saline with 2 ml water for injections. This should be combined with vigorous physiotherapy.
- HTS can be used as an adjunct to physiotherapy, and then 7% should be used. In those with severe airflow obstruction, or marked peak flow variability, it is wise to start with lower concentrations, but every effort should be made to work up to 7%; there is evidence that the plateau of the dose response curve is at 6-7% for mucociliary clearance. There is no benefit going to higher concentrations.
- The first line mucus clearance agent is rhDNase, but our data show that a third of rhDNase non-responders increase their lung function with HTS. The longer term Australian study showed clinically trivial improvements in lung function, but fewer infective exacerbations with HTS. The down side is two more nebulisers per day, which may not be feasible, especially if the patient is already taking nebulised antibiotics. HTS long term is therefore considered on an individual basis, especially for those with many infective exacerbations, who have not done well on rhDNase.

Frequently asked question: Will it work the same if I make up my nebulised antibiotics with HTS instead of normal saline? The answer is that there is no evidence that it will, and it could cause marked bronchoconstriction, so we do not advise this.

6.3.3 Mannitol

Inhaled dry powder mannitol is an osmotic agent that may increase mucociliary clearance in CF by improving cough clearance and rehydrating the airway surface liquid layer. NICE have reviewed this product and it is indicated when there is continued deterioration despite use of rhDNase or if there is intolerance of rhDNase and other osmotic agents ie: hypertonic saline are not appropriate.

6.4 AIRWAY INFLAMMATION AND IMMUNE MODULATION**6.4.1 Corticosteroids****Indications for oral steroids**

- Allergic bronchopulmonary aspergillosis
- Severe intractable bronchospasm / severe small airways disease
- Long term use as an anti-inflammatory agent in severe disease after careful consideration and discussion with patient

We tend to use prednisolone (note – enteric coated results in reduced absorption) treatment can be started with prednisolone 30mg - 40mg daily and reduced as soon as indicated

Indications for intravenous steroids

- In an acute exacerbation if the patient is very sick or not improving with antibiotics alone, we may use hydrocortisone (100-200mg daily), often together with aminophylline, both given intravenously. This reduces bronchospasm and inflammation.
- Intravenous methylprednisolone is used for severe intractable small airways disease after careful consideration and exclusion of NTM and aspergillus infection

Attention must be paid to potential adverse effects, particularly glucose intolerance as sometimes overt CF-related diabetes is precipitated. Patients must be told to report polyuria & polydipsia. Regular blood sugar monitoring is important. Patients must be warned of other potential side effects if long term steroid therapy is contemplated so they can make informed choices. Patients on long term steroids should have DEXA scans more frequently and give consideration to bone prophylaxis.

Indications for inhaled steroids

Symptomatic wheezing that requires regular bronchodilators, in a similar regimen to BTS guidelines for asthma. Ideally acute bronchodilator reversibility should be documented.

6.4.2 Long term Azithromycin

- Azithromycin is used as a long term immuno-modulatory agent
- Studies show improvement in FEV₁ and reduction of rescue antibiotic usage.

Dose:

500mg (if >40kgs) once daily on Monday, Wednesday and Friday

Side Effects:

Adults should be warned about the possibility of accumulation of azithromycin in the liver and the ear. Liver function tests should be performed at 1 month after starting Azithromycin and then at annual review. If tinnitus develops azithromycin should be stopped. Adult patients starting on azithromycin should have a baseline ECG.

6.5 OTHER LUNG COMPLICATIONS

6.5.1 Aspergillus (and other fungal) lung disease

Aspergillus fumigatus is a fungus that grows at 37°C. and the spores are of a size that they are deposited in the distal airways. The fungus produces a large number of toxic and allergenic exoproducts. There are a number of manifestations in CF, however in general, patients are advised to avoid mucking out stables, if they insist on horse riding this must be done out in the open.

Allergic bronchopulmonary aspergillosis (ABPA) is a serious potential cause of lung damage and is not uncommon in CF (prevalence varies 0.6 - 11%). Early pick-up depends on screening and high clinical suspicion. There are rare reports of an ABPA-like picture being a complication of other strains of *Aspergillus*, and other fungi, such as *Scedosporium apiospermum*.

Diagnostic criteria

This can be a very difficult diagnosis to make, because in the context of CF, most of the major and minor criteria can be positive in the absence of ABPA. Atypical cases may lack some or all of these criteria – maintain a high index of suspicion, and discuss with the Consultant if in doubt.

Clinical

- Increased wheezing/chestiness particularly if failing to respond to antibiotics and inhaled medications.
- Fever and malaise.
- Thick sputum with brown or black bronchial casts.

Investigations

Major Criteria

- CXR pulmonary infiltrates > 1cm diameter and segmental collapse.
- High serum IgE - especially an abrupt recent 4-fold rise to above 500 iu/ml, which falls with prednisolone therapy.
- High specific aspergillus IgE RAST. The normal value <0.35 iu/ml may rise 10-100x in ABPA.
- Positive aspergillus IgG (ICAP) >90 is positive in CF.
- Eosinophilia ($> 0.4 \times 10^9/l$).
- Positive skin prick test to aspergillus antigen (3mm > control).
- Reversible bronchoconstriction.
- Central bronchiectasis.

Minor Criteria

- *Aspergillus fumigatus* culture from sputum (NB found in 30% of all CF patients).
- Brown/black plugs in sputum.
- Late skin test reaction.

Treatment

Oral corticosteroids Prednisolone, given in the morning after food (not enteric coated as it is not well absorbed in CF) is normally used. Re-evaluate clinical response, CXR, and IgE. Dose is then gradually lowered over 4-6 months guided by clinical response and IgE. Relapse is common within 2-3 years of 1st episode, and often high doses of steroids are needed for a long time. Side effects are discussed in section above on use of steroids. An equivalent dose of dexamethasone may be used instead. Inhaled and nebulised corticosteroids are used by some, but not by us – there is no evidence for its use.

Pulsed methylprednisolone This is attractive for the non-compliant patient, and may have fewer side-effects, at the cost of more inconvenience. We use IV methylprednisolone ONCE per day for 3 days every month. Decision to use should be discussed with the consultant.

Itraconazole is used routinely for treatment of ABPA, in combination with oral or intravenous corticosteroids. The standard daily dose is 200 mg bd orally (monitor liver function) and continue whilst they remain on steroids. The capsules particularly are poorly absorbed so these should be taken with an acidic liquid (e.g. coca-cola, orange juice) and food. If possible use the liquid formulation, which is absorbed better although as it is quite unpalatable patients may refuse to take it! The liquid is taken on an empty stomach.

Itraconazole levels: See antimicrobial prescribing guidelines

Voriconazole is a newer oral antifungal antibiotic, which has better absorption than itraconazole and is not affected by gastric pH. Therefore it may be useful as a 2nd line agent for patients who have not responded to

or cannot tolerate twice daily itraconazole. Before changing to voriconazole in patients who do not respond to itraconazole, check to see if the itraconazole level is therapeutic (5-15mg/L). If not consider increasing the dose first. Voriconazole should only be started with consultant approval. Regular liver function tests are mandatory, and must not be forgotten. Side effects are not uncommon, including hair loss and skin photosensitivity (give advice about sun protection). We do not use intravenous voriconazole but long term IV use (>6 months) has been rarely associated with skin cancer.

Voriconazole levels: See antimicrobial prescribing guidelines

Posaconazole is used third line if patients do not tolerate Voriconazole

Nebulised amphotericin (non-liposomal) may be used in difficult cases at a dose of 5-10 mg twice daily after physiotherapy (check for bronchoconstriction and use bronchodilator pre-dose). The dose can be increased up to a total daily dose of 1mg/kg (max 25mg bd) depending on clinical response and tolerability. If it essential to use, and the patient does not tolerate the usual amphotericin, consider using nebulised liposomal amphotericin; note the high cost.

Other approaches: Occasionally we have used prolonged courses of intravenous Ambisome (liposomal amphotericin) in refractory cases. We also use IV caspofungin. Their use is a consultant decision. Caspofungin can be used for regular pulsed therapy when aspergillus also complicates NTM infection and maintenance rifampicin renders the use of 'Azol' drugs impossible. The anti-IgE monoclonal antibody omalizumab may rarely be considered; this is a consultant decision and funding application to the PCT will be needed.

Other manifestations of aspergillus lung disease

Invasive disease may occur, heralded by worsening of symptoms and progression of x-ray shadows, sometimes with cavitation, haemoptysis and pleuritic pains. Metastatic fungal spread is also possible in severely debilitated, immunosuppressed (including steroids) or neutropenic patients. CT scan is useful to confirm the diagnosis. Such cases warrant treatment with parenteral liposomal amphotericin (Ambisome) 5 mg/kg/day for 4 to 6 weeks or IV caspofungin.

Aspergillus bronchitis

We have recognised a syndrome as aspergillus bronchitis, this is characterised by the presence of persistent positive aspergillus cultures in association persistent cough and a raised IgG ICAP to aspergillus. This usually responds to antifungal therapy with itraconazole being first line followed by voriconazole.

6.5.2 Haemoptysis

Streaky haemoptysis is common with chronic infection but may indicate deterioration so sputum should be cultured and a course of antibiotics considered. Haemoptysis must be differentiated from haematemesis. The source is usually from areas of chronic airway inflammation. Massive, profuse haemoptysis due to vessel rupture can be life threatening (>250 mls/24 hours is the conventional level, but anything more than half a cupful over 24 hours merits referral). Bad haemoptysis is usually seen in patients with bad lung function, but has been reported in patients with normal spirometry. This occurs in 1% patients/year. The usual site of bleeding is tortuous bronchial arteries. The patient may experience a gurgling sensation which is a reliable lateralising symptom indicating the bleeding site. The patient is likely to be very scared - reassurance is essential. Primary management is resuscitation if needed (incredibly rare) - lay patient on side (gurgling side down), give oxygen. There is no evidence to suggest that stopping rhDNase is necessary, but if the patient is taking NSAIDs, stop them. Consider stopping hypertonic saline following massive haemoptysis if the HTS is causing more coughing. Physiotherapy may have to be adapted - seek advice from the Physiotherapist.

Investigations

- Hb & platelets.
- Coagulation.
- Group & save or cross-match blood.
- Sputum culture
- CXR can show new infiltrates but may not change and is of little use in localising the bleeding source.

Initial management

- Start intravenous antibiotics
- Oral or IV Tranexamic acid
- If coagulation defects are present ensure correction

Further management

Most bleeds will cease in response to this approach but if massive bleeding persists, or if repeated bleeding occurs over a short period (daily for 7 days with >100mls on 3/7 days) consider:

- **IV vasopressin** (Argipressin) is occasionally useful. **IV terlipressin** has fewer side effects; dose is 2mg then 1-2mg every 4-6 hours until bleeding is controlled, (maximum duration 72 hours).
- **Selective bronchial angiography and embolisation** can only be carried out by experienced interventional radiologists. Numerous dilated tortuous bronchial arteries are often identified some of which may take origin from aberrant sources. Actual source of bleeding is difficult to discern but generally a number of large vessels (>2.5mm) are embolised using variable sized gel foam pledgets. Great care to avoid spinal artery (with consequent paraplegia) and other systemic artery embolisation is necessary. Post embolisation pain requiring narcotic analgesia and transient dysphagia are common.

6.5.3 Pneumothorax

See BTS guidelines: (<http://www.brit-thoracic.org.uk/c2/uploads/PleuralDiseaseSpontaneous.pdf>).

A high index of suspicion is needed - consider the diagnosis if there is unexpected deterioration, unexplained chest pain, or worsening breathlessness. If in doubt, do a CXR but CT scan may be needed to detect it or determine optimal site for drain placement. The incidence of pneumothorax increases with age (overall 8%) and is a marker of severe lung disease. It carries a bad prognosis, particularly if the chest drain cannot be rapidly removed. All but the most trivial pneumothorax in a stable patient mandates admission to hospital.

A tension pneumothorax is an emergency that requires urgent treatment with a chest drain, regardless of the CF. A small asymptomatic pneumothorax can be managed by observation alone and may resolve but in an already hypoxic patient, such a leak may cause decompensation. If the patient is decompensating or has a large pneumothorax, management includes -

- Monitor SpO₂ and give oxygen (check for CO₂ retention).
- Intercostal chest drain.
- Local anaesthesia and subsequent oral analgesia.
- Antibiotics (IV antibiotics are prudent in all but the most trivial pneumothoraces).
- Physiotherapy must be continued whilst the chest drain is in. The physiotherapist will adjust techniques accordingly.

Slow resolution of a pneumothorax requires careful management and discussion with the thoracic surgeons. Management will be consultant led.

Remember also guidelines about flying after a pneumothorax – need to wait at least six weeks:
<http://www.brit-thoracic.org.uk/c2/uploads/FlightRevision04.pdf>

7: NUTRITIONAL AND GASTROINTESTINAL CARE

7.1 NUTRITIONAL CARE

- Survival in cystic fibrosis is hugely dependent on nutritional status. Poor nutritional status is a significant independent risk factor for poor survival and early death in cystic fibrosis.
- Good nutritional status can and should be achieved in the majority of patients with cystic fibrosis by combining a high calorie diet with adequate pancreatin supplements. However, for some patients nutrition will remain a problem.
- Poor nutrition can be due to a variety of reasons including increased stool energy losses, anorexia and poor dietary intake, increased energy demands of the disease, abnormal adaptive response to malnutrition and the increase in energy demand of cystic fibrosis treatment.
- An alternative means of improving nutrition can be achieved through the use of dietary supplements and in some who require a more invasive form of nutrition therapy; supplementary enteral tube feeding or parenteral feeding. All these treatments can be used for short term and long term use.
- Supplementary nutritional therapy has been shown to benefit nutritional status and improve pulmonary function.

7.2 NUTRITIONAL ASSESSMENT

- The BMI (body mass index) ($\text{weight [kg]}/\text{height [m]}^2$) is a simple and easy way of assessing nutritional status. It assesses whether weight is in proportion to height and therefore gives an indication of body fatness or thinness.
- BMI is the routine method of nutritional assessment undertaken for adult cystic fibrosis patients.
- Weight is taken on every clinic visit, inpatient admission and at annual review so that BMI can be calculated and nutritional assessment can be carried out by the dietitian during any consultation. BMI provides the dietitian with an indication into the degree of nutrition support required for a patient.

Criteria for different stages of nutritional intervention

Nutritional Indices	>18 years of age
Normal nutritional state – preventative counselling	BMI 19-25 and/or no recent weight loss
Dietetic referral indicated – consider supplements	BMI <19 or 5% weight loss > 2 months
Aggressive nutritional support	Supplements tried and either BMI <19 or > 5% weight loss over >2 months

- The aim of nutritional therapy is to achieve a healthy BMI (19-25kg/m²). An optimal BMI of 22-23kg/m² allows room for weight fluctuations up or down.
- To achieve optimal nutritional status individual nutritional requirements are calculated however, the majority of cystic fibrosis adult patients require between 120-150% of the EAR (Estimated Average Requirements) and 200% the RNI (Reference Nutrient Intake).

Cystic fibrosis adult nutritional requirements

Energy and Protein Requirements in Cystic Fibrosis								
	DRV (EAR's)		120%		150%		X2 RNI Protein	X2 RNI Protein
Age	Male	Female	Male	Female	Male	Female	Male	Female
15-18	2755	2110	3306	2532	4132	3165	110	90
19-49	2550	1940	3060	2328	3825	2910	110	90
50-59	2550	1900	3060	2280	3825	2850	106	92
60-64	2380	1900	2856	2280	3570	2850	106	92

7.3 ACHIEVING THE NUTRITIONAL NEEDS OF ADULT CYSTIC FIBROSIS PATIENTS

7.3.1 Diet

- A high calorie diet is required by the majority of adult cystic fibrosis patients to meet nutritional needs. This is often hard to achieve as many patients experience reduced appetite particularly during episodes of infection; the time at which the body's energy requirements are at their highest.
- Other factors which often challenge a patient's ability to meet their nutritional requirements and follow a high calorie diet include poor lung function or recurrent chest exacerbations, excessive cough, increased sputum production, gastro-oesophageal reflux, nausea and vomiting, psychosocial issues for example depression and disordered eating behaviour, a dislike to high energy foodstuffs and gastrointestinal disturbances including constipation, DIOS (Distal Intestinal Obstructive Syndrome), abdominal pain, distension and bloating.
- To optimise nutritional status a diet high in energy and protein, individually tailored to meet nutritional requirements is carefully devised by formulating a nutritional care plan for each individual.
- A diet high in calories, protein and fat is encouraged to meet energy needs. Liberal use of high fat, high calorie and high protein snacks for example fried foods should be encouraged particularly if weight is poor.
- Food fortification which advocates the addition of butter, olive oil and full fat dairy products such as cheese and cream to foods and the encouragement of small frequent meals and snacks should also be advised to encourage weight gain.

Cystic Fibrosis Diet

Nutrient/ Food	Cystic Fibrosis Diet
Energy	Individually tailored. 120-150% Estimated Average Requirement (EAR – of normal) depending on nutritional state.
Fat	40% of total energy intake
Refined Sugars	Allow throughout the day
Carbohydrate	45-50% of total energy intake
Dietary Fibre	Encouraged in the well nourished. In the poorly nourished patients fibre may compromise energy intake.
Protein	200% of Reference Nutrient Intake (RNI) 15-20% of total energy intake
Salt	Increased requirement
Snacks	Ad-lib

7.3.2 Oral Nutritional Supplements

- Nutritional failure in cystic fibrosis is multifactorial and management includes optimising oral intake, reviewing the adequacy of pancreatic enzyme therapy, treatment of the chest, exclusion of cystic fibrosis-related diabetes mellitus and any gastrointestinal causes including coeliac disease and lactose maldigestion before embarking upon invasive nutritional support.
- When considering oral nutritional supplements it is important to be aware that there are a wide variety of different supplement preparations available including, energy only supplements for example glucose polymers and fat emulsions, energy and protein rich supplements and nutritionally complete supplements. The type and quantity prescribed should be assessed on an individual basis and the choice is usually dependent on a patient's age, preference and nutritional requirements.
- Nutritional supplements should compliment a patient normal dietary food intake not replace food so timing and quantity of supplements is important and advice on taking supplements after a meal or in between as a snack should be encouraged so the appetite for normal food is not replaced.
- Taste fatigue can often be reported with long term use of oral nutritional supplements so altering the flavour and type of supplement periodically may be useful to prevent taste fatigue occurring.
- Supplements can be used creatively and dietitians' can provide recipes ideas and show ways of incorporating supplements into cooking to encourage supplement intake and prevent taste fatigue.

Adult Oral Nutritional Supplements

Type Supplement	Name of Supplement	Supplement Manufacturer
Milk Based Supplements (1.5-2.6kcal/ml)	Build Up Milkshake Resource Resource Energy Resource 2.0 Resource Protein Extra Clinutren 1.5	Nestle
	Ensure Plus Ensure Plus Fibre Ensure Plus Yoghurt Ensure TwoCal Enshake	Abbott
	Fortisip Fortisip Multi Fibre Fortisip Extra Fortifresh Yoghurt Style Fortisip Compact Scandishake Fortimel	Nutricia
	Fresubin Fresubin Energy Fresubin Energy Fibre Fresubin Protein Energy Fresubin 2Kcal Calshake Providextra	Fresenius Kabi
	Complan Milkshake	Complan
	Clinutren Fruit * Resource Fruit * Clinutren Fruit *	Nestle
	Ensure plus Juice *	Abbott
Juice Based Supplements	Fortijuce *	Nutricia
	Provide Xtra	Fresenius Kabi
	Build up soup	Nestle
	Complan Soup	Complan
Soup Supplements		

Custard/ Pudding Style Supplements	Clinutren Dessert	Nestle
	Forticreme	Nutricia
	Ensure Pudding	Abbott
	Fresubin Creme	Fresenius Kabi
Carbohydrate/ Fat/ Protein Liquid Polymers	Calogen	SHS
	Fresubin 5Kcal Shot	Fresenius Kabi
	Polycal Liquid *	Nutricia
	ProCal Shot	VitaFlo
	Calogen Extra	SHS
	Liquigen *	SHS
	Liquid Duocal	SHS
Carbohydrate / Protein Powdered Polymers	Polycose *	Abbott
	Super Soluble Maxijul *	SHS
	Polycal Powder *	Nutricia
	Caloreen *	Nestle
	Super Soluble Duocal	SHS
	Procal Powder	VitaFlo

*** Do not require pancreatic enzymes**

7.4 ENTERAL FEEDING

- Nasogastric (NG) or gastrostomy (PEG) feeding should be considered when an adult cystic fibrosis patient has a BMI less than 19 or more than 5% weight loss over 2 or more months or has failed to gain weight during pregnancy despite oral nutritional supplements (*see Criteria for different stages of nutritional intervention*).
- Positive changes in body composition, increased muscle strength, growth velocity and an increase in the patients' ability to participate in activities of daily living has been associated with enteral feeding. Additionally improvements in weight, nutritional status and the stabilisation or reduced rate of decline in lung function has been shown to improve with enteral feeding in cystic fibrosis patients.
- Long term enteral feeding can help provide a lasting benefit and help achieve and maintain optimal nutritional status for patients unable to meet their energy requirements with adapted dietary intake and oral nutritional supplements.
- Prior to deciding whether to have a NG or PEG placed the patient and family should be informed about why feeding is important and how it will be of benefit, the different types of feeding available, delivery systems, how tubes are placed, frequency of feeding and arrangements of home feeding.
- The main routes of enteral feeding are with Nasogastric tubes (NGT) or gastrostomies (PEG/ Button). For the majority gastrostomies are the route of choice for most cystic fibrosis adults. Within the Royal Brompton and Harefield NHS Foundation Trust these are placed percutaneously by endoscopic placement (PEG) however gastrostomies can be placed radiologically (RIG) or surgically as or if required.

7.4.1 Nasogastric Feeding

- Nasogastric feeding is simple and can be used successfully for short term support during respiratory exacerbations as an episodic nutritional boost or as a trial prior to gastrostomy feeding. It is also a useful method for those unable or at high risk to have a PEG placed due to anatomical reasons (oesophageal or gastric varices) or physiological reasons (very low weight, poor lung function). NG can be useful and of benefit in these situations although success generally depends on attitude. Many patients however prefer this route of feeding because of concerns over body image.
- It is generally easy to train patients to pass their own NG tubes and this should be encouraged particularly when considering nocturnal feeding as patients can pass an NG tube in the evening and remove upon waking which allows the patient freedom during the daytime.

- The insertion of NG tubes may however prove too difficult for some (difficult to pass due to nasal polyps), in which case nurses on the ward during inpatient admissions can place the NG tube and this will then be left in place for a period of weeks or months at a time. For a short term nutritional boost this is also the preferred method.
- Fine bore NG tubes (usually 8 French) should be used where possible. They can be left in situ for up to 2 months or longer if polyurethane tubes are used. PVC tubes should be replaced every 10-14 days.
- Once in situ, NG tubes are rarely uncomfortable and will not interfere with eating in the daytime or any other normal daily activities.
- The main disadvantage of NG feeding is coughing which may displace the tube or cause difficulty swallowing enzymes with the tube in situ. If NG feeding is unsuccessful, not well tolerated or long term support is envisaged, gastrostomy insertion should be considered.
- For tube care, problem solving, procedures for administration of feeds refer to the Policy and Procedures on Adult Enteral Feeding which can be found under policies on the Trusts Intranet.

7.4.2 Gastrostomy Feeding

- Gastrostomy feeding is the preferred method of long term nutritional support. Overnight feeding may be more comfortable overnight via a gastrostomy than via a NGT particularly during respiratory exacerbations. Additional bolus feeding can also be given during the day if required.
- Gastrostomy tubes are currently placed endoscopically at Chelsea and Westminster Hospital by Gastroenterologists under sedation (local) although general anaesthetic may be occasionally preferable for those known to struggle with endoscopic procedures.
- Prior to gastrostomy placement patients are usually admitted for prophylactic intravenous antibiotics before anaesthesia and patients should also have ambulatory pH measurements or contrast studies carried out as enteral feeding is known to increase gastro-oesophageal reflux.
- Immediately post procedure patients may experience some pain, this may occur due to their stronger toned abdominal muscles as a result of daily physiotherapy and coughing. Other complications include increased cough and fall in lung function following anaesthesia which may prolong hospital stay and need for intravenous antibiotics. Peritonitis is more serious but a relatively uncommon complication of PEG placement.
- It is usual for patients to stay for several days post PEG placement procedure where they may require pain relief for physiotherapy. They will also need time to learn the technique and for home enteral feeding arrangements to be organised. It is also important post PEG placement that the patient is monitored for glucose intolerance and/or development of cystic fibrosis-related diabetes as insulin may be required to prevent hyperglycaemia during the enteral feeding period.

Types of gastrostomies

- Percutaneous gastrostomy tubes (PEGs) are currently usually placed initially in cystic fibrosis patients. These tubes have a life expectancy of up to and beyond 2 years after which time they need replacing endoscopically.

Percutaneous Endoscopic Gastrostomy (PEG)



- Approximately three months post initial PEG placement patients have the choice to replace their PEG with a low profile device or button, which once placed initially in the ready-formed tract via endoscopy has the advantage of being placed and removed manually by the patient without sedation, any pain or discomfort.
- The balloon button contains water (usually 5mls). If the balloon bursts the patients cannot aspirate any water, this indicates the need for replacement.
- Balloon buttons generally need to be changed approximately every 3-6 months.
- It is common practice to establish a tract initially via PEG placement for approximately 3 months prior to button insertion however recent papers have suggested a button can be inserted as a primary procedure, which may reduce the potential morbidity of a second procedure in this high risk group of patients. The Royal Brompton and Harefield NHS Foundation Trust are currently in its early stages of implementation with Chelsea and Westminster Hospital with regards to placement of buttons as first line procedure.
- Balloon buttons have a limited lifespan in cystic fibrosis patients but ease of replacement counteracts this disadvantage. There are a variety of different types (Mini, Mic-Key, Nutriport) available which come in a range of different sizes and shapes. Generally any one of these balloon buttons can be chosen for placement for any patient, however the supply of balloon buttons is variable and arranged on an individual basis.

Low profile device buttons



Care of the gastrostomy

- Following placement of a gastrostomy, it is important to keep the site clean, dry and open to air. For the first 2-3 weeks the gastrostomy is usually not moved and should not be immersed in water.
- The tube should be rotated according to manufacturers guidelines (rotate 360 degrees and push in and out) and flushed with at least 10ml of sterile water prior to and following each feed/ medication (liquid only). Sticky PEG sites should be swabbed for bacterial and fungal culture and topical antimicrobial therapy prescribed. Antibiotic and steroid combinations may be effective where antibiotics alone have failed.
- For problem solving with gastrostomies the patient is advised to contact their home enteral feeding nurse or district nurse for whom they will have received contact details for when they had their gastrostomy originally placed. If the problem does not resolve then it is advisable that the cystic fibrosis team liaise with Dr Steel Consultant Gastroenterologist or associate colleague at Chelsea and Westminster Hospital.

7.4.3 Timing of Enteral Feeding

- Timing of feeding is very important and should be adjusted according to the patient's lifestyle. The majority of patients are encouraged to feed nocturnally for usually 8-10 hours with 1-2 hour break in the morning for physiotherapy.

- Nocturnal feeding helps prevent daily activities being disturbed and encourages a continued high energy diet so as not to risk reducing appetite and encourage normal eating behaviour in the day time. Some patients will receive a combination of nocturnal feed and daytime bolus feeding or just daytime bolus feeding for those who are unable to tolerate nocturnal feed.
- Complications with enteral feeding generally tend to be nausea, bloating, vomiting and occasional diarrhoea. Manipulation of the rate, type or timing of feed, the use of antiemetics and pro-kinetics are useful to reduce bloating and prevent early morning vomiting and ensuring the optimal dose and timing of pancreatic enzyme therapy is being used usually resolves any enteral feeding complications.
- For further enquiries regarding gastrostomies and feeding consult the Policy and Procedures on Adult Enteral Feeding on the Trust Intranet.

7.4.4 Enteral Feeds

- Initiation of enteral feeds takes place immediately following confirmation of correct NG placement and within 6-12 hours for the uncomplicated PEG placements. Feed is then gradually increased at an individual rate as tolerated until the desired intake is reached. Generally 40-50% of a patient's nutritional requirements are provided via enteral feeding.
- There are a wide variety of feeds available for enteral feeding. High energy polymeric feeds that contain the most calories and protein per volume are generally the feed of choice in adult cystic fibrosis patients (2-2.4kcal per ml feeds) and are tolerated well. They are all pre-constituted with some contained within a ready to hang container and others presented in individual bottles (they are multipurpose –used orally and enterally and require decanting into a larger ready to hang containers prior to use). The type of feed chosen is assessed on an individual basis taking into consideration the patients nutritional requirements, clinical condition and lifestyle.
- The majority of patients tolerate high energy polymeric feed however if the patient fails to gain weight and is struggling to meet their nutritional goals despite the enteral feed rate, volume and timing of feed being reviewed and cystic fibrosis-related diabetes, adherence, and enzyme dose excluded as an alternative cause, than elemental or semi elemental feeds should be considered.
- Elemental feeds are generally lower in fat and contain a mixture of medium and long chain triglycerides, have a high osmolality and lower calorie density. Enzymes can be given in the more complicated patients but are generally not necessary.
- There are few reports comparing the efficacy of elemental vs polymeric feeds but it is thought that steatorrhoea is no greater with polymeric feeds when enzymes are given than compared with giving an elemental feed.
- High fat feeds which result in less carbon dioxide production and lower respiratory quotient have been advocated for cystic fibrosis patients with severe lung disease however current work carried out on carbohydrate loading found that even with the increase in carbon dioxide after a high carbohydrate formula patients who were clinically stable were able to increase their minute volume sufficiently to prevent worsening hypoxia or carbon dioxide retention. High fat feeds for cystic fibrosis are currently not routinely used within our trust.

Adult enteral feeds available

Type of Enteral Feed	Name of Enteral Feed	Manufacturer
Polymeric 1.0 kcal/ml	Jevity Jevity Promote Jevity Plus HP Osmolite Osmolite Plus Osmolite HP	Abbott
	Nutrison Nutrison 1000 Complete Multi Fibre Nutrison Multi Fibre	Nutricia
	Fresubin Original and or Fibre Fresubin 1000 Complete	Fresenius
Polymeric 1.2-1.5kcal/ml	Fresubin 1200/1500/1800 Complete Fresubin Energy and/or Fibre	Fresenius
	Jevity 1.5kcal Osmolite 1.5kcal	Abbott
	Peptamin 1.5	Nestle
	Nutrison Energy	Nutricia
	Nutrison Energy Multi Fibre	Nutricia
High Energy Polymeric 2-2.4kcal/ml	Ensure TwoCal	Abbott
	Nutrison Concentrated	Nutricia
	Fresubin 2250 Complete	Fresenius
Semi Elemental and Elemental	Perative *	Nestle
	Elemental 028 * Elemental 028 Extra * Emsogen *	SHS
	Peptamin * Perative *	Nestle
	Nutrison MCT *	Nutricia
Specialist Feeds	Oxepa Pulmocare Suplena	Abbott
	Nutrison Peptisorb Nutrison Soya and/or Multi Fibre Nutrison Low Sodium Nutrison Protein Plus and/or Multi Fibre	Nutricia
	Fresubin HP Energy Fresubin Soya Fibre Reconvan Survimed OPD	Fresenius

*** Pancreatic enzymes may not be required in the non complicated patients**

7.5 PARENTERAL NUTRITION

- Parenteral nutrition has been advocated as a useful option for short term treatment to improve or maintain nutritional status and lung function post surgery, prior to transplant and/or where enteral feeding is not possible.
- Although parenteral nutrition has been shown to be successful in these situations it has few benefits over enteral nutrition. The cost, risk of complications and complexity of administering parenteral nutrition means that it is not a routine therapy for patients with cystic fibrosis.
- Parenteral nutrition requires a sound knowledge and application of the principle of fluid and electrolyte maintenance. Histologic changes within the liver cells can occur within just 1-2 weeks after initiation of parental nutrition. Hyperglycaemia, hypoglycaemia, essential fatty acid deficiency, hypokalaemia and hyperlipidaemia are other complications that may also occur with parenteral feeding.

7.6 APPETITE STIMULANTS AND ANABOLIC HORMONES

Megestrol acetate (Megace®) is an appetite stimulant which has been used in cystic fibrosis patients with a poor appetite and has been shown to improve weight and respiratory function. It has and is used within our trust for specific cystic fibrosis patients who have a poor nutritional status due to a low appetite and inadequate oral intake.

Anabolic agents have been explored in cystic fibrosis. Growth hormone has been shown to lead to weight gain and growth. Creatine supplementation has been shown to increase muscle strength, patients well being and body weight. Currently anabolic agents are not encouraged or advocated in cystic fibrosis patients as only small studies have examined adjunctive drugs which have expressed that some undesirable side effects can occur. It is generally agreed that larger clinical trials are warranted before these products can be safely and routinely administered to patients.

7.7 MALABSORPTION AND PANCREATIC ENZYME REPLACEMENT THERAPY (PERT)

The major factor causing malabsorption in cystic fibrosis is deficiency of pancreatic enzymes. Pancreatic insufficiency is present in 85% of cystic fibrosis patients, but 99% of $\Delta F508$ homozygotes'. Pancreatic insufficiency is most often present from birth and if left untreated leads to severe malabsorption of fat and nitrogen, malnutrition and growth failure. Nonetheless some 40-50% of ingested dietary fat is absorbed without treatment. This is probably due to the action of lingual and gastric lipase. Carbohydrate malabsorption is minimal.

In approximately 15% of cystic fibrosis individuals, pancreatic changes are less severe and sufficient functional pancreatic exocrine tissue remains to allow normal fat and protein digestion. However such pancreatic sufficient individuals do not as a group have normal pancreatic exocrine function. Patients who are pancreatic sufficient have been reported to have better nutrition and improve prognosis regarding development of respiratory disease.

Due to the progressive nature of pancreatic damage; with increasing age, pancreatic sufficient individuals can eventually become pancreatic insufficient particularly if they have "severe" mutations including *F508del*.

Pancreatic insufficient patients require pancreatic enzyme replacement therapy to prevent and control symptoms of malabsorption and to achieve or maintain optimal nutritional state. If uncontrolled,

malabsorption results in abdominal pain, frequently oily pale and offensive stools, poor growth, malnutrition and deficiency of fat soluble vitamins. If these symptoms appear apparent in pancreatic sufficient patients then it is important to investigate for pancreatic insufficiency.

Assessing pancreatic function

There are many different methods of assessing intestinal malabsorption and pancreatic abnormality. The gold standard for measuring fat absorption is an assessment of the fat excretion over 3 days and its relation to dietary fat intake over the same time period however this method is largely impractical and very rarely used within our trust.

Pancreatic insufficiency is routinely confirmed within the Trust using a faecal pancreatic elastase 1 (Faecal elastase test). This is carried out before pancreatic enzyme replacement therapy is commenced. This test is not affected if patients are already taking pancreatic enzymes.

Stool samples for faecal elastase are sent to Biochemistry who requests it to be assayed in the Virology Department of Sandwell and West Birmingham City Hospital.

Faecal Elastase

Normal	>200 mcg/g stool
Mild/ Moderate pancreatic insufficiency	100-200 mcg/g stool
Severe pancreatic insufficiency	<100 mcg/g stool
“Typical” CF pancreatic insufficiency	<15 mcg/g stool

7.7.1 Pancreatic Enzymes

- All pancreatic insufficient patients should receive enteric coated acid resistant pancreatic enzyme preparations. The enteric coating protects the enzymes from denaturing by gastric acid. Enteric coated pancreatic enzymes are available as microspheres, micro tablets, granules and powders. The preferred method of administration for adult cystic fibrosis patients is with microspheres using Creon (Solvay) capsules. Creon is available in varying strengths ranging from 5000 – 40,000 IU (units) lipase per scoop or capsule.
- Individual requirements for pancreatic enzymes varies widely which reflects the differing degrees of residual pancreatic function, the type of enzyme preparation and patho-physiological factors such as intestinal pH hence, pancreatic enzyme dose is assessed on an individual basis.
- There are also various guidelines for use of pancreatic enzymes because although the coefficients of fat absorption between 85%-95% should be possible with the current enzyme preparations, a substantial number of patients with cystic fibrosis remain unable to achieve normal absorption.
- A standard starting dose of pancreatic enzyme therapy suggests 1-2 capsules of standard pancreatin preparation (Creon 10,000 capsules) per meal and half to one capsule with fat containing snacks or 500 units of lipase per kilogram body weight per meal and half of this dose per snack. Creon should be taken with each fat or protein containing meal, snack or drink but it is not required with juices, fizzy drinks, squash, fruit (except avocados), vegetables, jellies, sugar, jam, honey, syrup, fruit lollies and boiled/ jellied sweets.
- It is advised generally that enzymes are administered at both the beginning and during the meal to ensure thorough mixing of enzymes and meal throughout its small intestinal passage. There is also evidence to suggest that there are differential rates of gastric emptying between individuals, however a simpler

- Ideally meals should be consumed within 30 minutes however this may not be practical for some patients who have a poor appetite. In this case additional enzymes may be given towards the end of a meal or between the main course and pudding.
- Enzyme capsules should be swallowed whole, kept at room temperature and the expiry date should not be exceeded to prevent loss of enzymatic activity and ensure optimal efficacy.
- The eventual established dose required largely depends on the fat content of the food or drink taken alongside stool pattern and evidence of steatorrhoea. Dosages are adjusted upwards to achieve normal or near normal stool pattern with formed, non greasy stools of normal odour and absence of abdominal pain or excessive and malodorous flatus.
- Dose requirements can vary widely between 500-4000 IU (units) per gram of dietary fat. Prescriptive recommendations have suggested pancreatic enzyme dose should be based on 500-2500 units of lipase per kilogram of body weight per meal and there are recommended safe upper limits of 10,000 units of lipase per kilogram of body weight per day or less than 4000 units of lipase per gram of dietary fat per day to prevent the risk of fibrosing colonopathy. However it is important to understand that in some cases dietary fat intake can be very high so enzyme requirements may be slightly greater than the recommended maximum enzyme dose. So it is always advisable that enzyme dosing is tailored according to the patient clinical status, symptoms and nutritional need.
- An experienced cystic fibrosis dietitian is required to educate patients about dose adjustment and timing of pancreatic enzyme therapy to achieve optimal absorption. The dietitian assesses a patient's individual nutritional needs and reviews and modifies appropriate treatment plans regularly according to the changing clinical and psychosocial needs of the patient.
- Even when clinical symptoms appear to be controlled by pancreatic enzyme replacement therapy many patients still have a significant degree of fat malabsorption. The control of gastrointestinal signs and symptoms is not always indicative that malabsorption is controlled. Persisting gastrointestinal symptoms in the face of apparently reasonable doses of enzymes may not be due to inadequate enzyme dose or inadequate timing but some other cause.
- A progressive increase in enzyme dose without further investigation is not recommended. In this case the degree of residual malabsorption should be estimated using stool microscopy for fat globules and/ or assessing the levels of serum fat soluble vitamins. Other gastrointestinal disorders should also be considered as deficiency of pancreatic enzymes is the most important but not the only factor responsible for malabsorption in cystic fibrosis.
- Gastro-oesophageal reflux is relatively common in cystic fibrosis and it has been shown that a reduction in gastric acid using proton pump inhibitors – omeprazole, ranitidine, lansoprazole has been shown to improve absorption in patients where control of malabsorption was poor even with enteric coated resistant enzymes.
- Other possible gastrointestinal complaints that should be excluded include inflammatory bowel disease, pancreatitis (in pancreatic sufficient patients), short bowel with bacterial overgrowth and adhesions after intestinal surgery, liver and gallbladder disease, lactose maldigestion or cows milk protein allergy, crohns disease and coeliac disease.
- Patients' adherence to treatment is the most common cause of ongoing significant fat malabsorption despite optimal enzyme dosing and this provides another problem in the control of gastrointestinal symptoms. The dietitian has a role to play in discussing practical details with patients to overcome these issues.

7.7.2 Pancreatic enzyme therapy and enteral feeding

- An initial dose based on the number of enzyme capsules taken for a main meal is advised with adjustments according to bowel symptoms and weight gain. The enzyme dose is worked out on an

- Elemental feeds are usually lower in fat and contain a mixture of medium and long chain triglycerides. There is ongoing consideration over whether these feeds require pancreatic enzymes or not however the current consensus states there is insufficient evidence to advise whether enzymes are necessary with elemental feeds.
- There is currently insufficient evidence as to the optimum time for enzymes to be taken with feeds. Patients are advised to give half the recommended dose at the beginning of the feed and the remaining half mid-feed however generally as feeds are administered overnight it is only practical to give the second half at the end of the feed. It is not routine practice to wake patients to take enzymes. Enzymes are always taken orally if able. Granule/powdered enzymes should be administered down enteral tubes in circumstances where a patient is ventilated and sedated.
- Enzyme efficacy can be improved by using proton pump inhibitors or H₂ antagonists to reduce gastric acid output.
- In this situation an enteric coated formula called Creon Micro (5000 IU (units) of lipase per scoop) is flushed down nasogastric or gastrostomy tubes with water every 2-4 hours if the feed is being administered continually. If problems with tube blockage occur CreonMicro can be dissolved in bicarbonate of sodium solution or alternatively a powdered enzyme powder (Pancrex powder) can be mixed with water and flushed down the enteral feeding tube.

7.8 FAT SOLUBLE VITAMINS

Malabsorption of fat soluble vitamins is likely in most patients with cystic fibrosis particularly those who are pancreatic insufficient. Low vitamin levels are associated with poorer clinical status and reduced lung function.

Routine vitamin supplementation is commenced upon diagnosis of pancreatic insufficiency. Vitamin supplementation alongside improved pancreatic enzymes and normal to high fat diets helps to reduce the incidence of fat soluble vitamin deficiency with cystic fibrosis. Those patients with poorly controlled malabsorption, liver disease, late diagnosis, bowel resection or who adhere poorly to therapy remain at risk of clinical deficiencies of fat soluble vitamins.

Plasma vitamin levels are monitored annually as part of the annual review and vitamin supplement dose is adjusted according to plasma levels as necessary. The affects of alterations to therapy is checked after 3-6 months. Pancreatic sufficient patients also have their serum fat soluble vitamin levels checked at annual review and supplemental vitamin A, D, E and K commenced when low levels are detected or as clinically indicated.

Empirically, the aim is to achieve plasma levels of vitamin A, D, E and K at the upper limit of the normal range.

Daily vitamin dose recommendations from the Cystic Fibrosis Trust Working Group:

Age	Vitamin A 1 µg = 3.3 IU	Vitamin D 1 µg = 40 IU	Vitamin E 1 mg = 1.5 IU	Vitamin K
Adults	1200-3000 µg 4000-10000 IU	20-50 µg 800-2000 IU	100-200 mg 150-300 IU	10 mg

Fat soluble vitamins can be taken at any time in those that are pancreatic sufficient. In pancreatic insufficiency pancreatic enzyme replacement therapy may enhance absorption of the fat soluble vitamins. It would appear logical for vitamin supplements to be taken at meal times with pancreatic enzymes.

7.8.1 Vitamin A

- Plasma vitamin A levels have been found to be lower in both pancreatic insufficient and sufficient cystic fibrosis patients compared with healthy controls.
- Vitamin A is important for vision, integrity and proliferation of epithelial cells and immunity. Low vitamin A levels are associated with poorer clinical status and impaired lung function.
- Vitamin A deficiency may be multifactorial in cystic fibrosis and not simply a consequence of malabsorption. Increased retinol faecal loss, possible defect in the handling of retinol by the gastrointestinal tract, reduced mobilisation from liver stores, low plasma levels of retinol binding protein and zinc may all contribute to hypovitaminosis A.
- Measurement of plasma retinol is unreliable; there is a poor correlation between clinical and biochemical findings. There is also no feasible way of assessing if vitamin A is accumulating in the liver as liver stores cannot be accurately assessed in living subjects. Plasma retinol concentrations can also be depressed during acute infection highlighting the need for checking levels during periods of clinical stability.
- Retinol binding protein can help interpret plasma vitamin A levels as it transports plasma vitamin A. Retinol binding protein can be suppressed when zinc deficiency is present so zinc supplementation is sometimes warranted.
- Vitamin A can cause toxicity and there have been suggestions that hypervitaminosis A contributes to reduced bone mineral density so doses should be increased with caution.

7.8.2 Vitamin E

- Overt clinical symptoms of vitamin E deficiency are rare in cystic fibrosis.
- Vitamin E or alpha-Tocopherol accounts for 90% of vitamin E present in human tissues. It is a powerful antioxidant which protects lipoproteins and cellular membranes against destruction. It may have a role in protecting against oxidative lung damage and progression of lung disease in cystic fibrosis patients because of its antioxidant properties.
- Long standing severe vitamin E deficiency can result in irreversible neurological damage, haemolytic anaemia, neuromuscular degeneration and retinol and cognitive deficits.
- Serum or plasma vitamin E represents only a small proportion of total body vitamin E. Levels are measured alongside vitamin E/fasting lipid ratio as serum vitamin E levels also vary according to the levels of carrier lipoprotein.
- Larger doses have been tolerated without adverse effects in studies however safe upper level for supplementation is yet to be determined.
- It is thought that cystic fibrosis patients may have inadequate antioxidant defences to cope with elevated oxidative stress, which they regularly experience. It has been suggested that current doses of vitamin E may be too low.

7.8.3 Vitamin K

- There is an increased risk of developing vitamin K deficiency in cystic fibrosis due to fat malabsorption, bile deficiency, liver disease and antibiotic therapy.
- Vitamin K is required for the formation of osteocalcin which is involved in bone metabolism. It is thought that sub clinical deficiency of vitamin K can increase the risk of cystic fibrosis patients developing osteopenia and osteoporosis.
- Measurement of PIVKA II (prothrombin induced vitamin K absence) levels has shown that vitamin K deficiency is common in cystic fibrosis pancreatic insufficient patients.

- Under carboxylated osteocalcin levels that measure the adequacy of vitamin K status for bone metabolism have also been reported as abnormal.
- Patients' vitamin K status is not currently assessed because plasma vitamin K is unreliable for assessment of status and PIVKA II and osteocalcin measurements are not routinely available within the United Kingdom.
- A recommended dose of vitamin K for cystic fibrosis has not yet been established yet there are a number of suggestions for routine supplementation of vitamin K.
- Suggested doses set out in by the Cystic Fibrosis Trust recommend 10mg daily, as studies using lower doses found it was ineffective in improving PIVKA II levels. Metabolic turnover of vitamin K is every 24 hours hence the recommendation of a daily vitamin K dose.
- We recommend vitamin K supplementation of 10mg daily for pancreatic insufficient patients.

7.8.4 Vitamin D and Bone Mineralisation

- There are two main forms of vitamin D; Ergocalciferol (D2) and Colecalciferol (D3).
- The prevalence of vitamin D deficiency in Cystic Fibrosis has been reported to be as high as 90%. There is a wealth of literature to support that vitamin D deficiency in cystic fibrosis is a worldwide issue which affects all age groups particularly those with pancreatic insufficiency.
- Vitamin D deficiency in CF is thought to be due to reduced levels of vitamin D binding protein coupled with reduced absorption and hydroxylation of vitamin D. PI also increases the risk of vitamin D deficiency by reducing absorption of dietary fat and fat soluble vitamins.
- Inadequate body fat due to malnutrition can result in inadequate storage of vitamin D particularly in winter and that coupled with lack of sunlight exposure can increase the risk of vitamin D deficiency.
- Vitamin D deficiency has been shown to contribute to bone disease in CF. The aetiology of CF-related low bone mineral density is multi factorial and is attributed by pancreatic insufficiency, cystic fibrosis related diabetes, inflammatory cytokines, cystic fibrosis related liver disease, lack of weight bearing exercise, glucocorticoid use, malnutrition, calcium deficiency and vitamin K deficiency.
- CF-related low BMD is a common complication of long term survivors of cystic fibrosis and it is well documented that adults with cystic fibrosis have low bone mineral density and a high prevalence of osteopenia and osteoporosis.
- Low bone mineral density can result in skeletal pain, muscle weakness and pathological fractures. Increased prevalence of rib and vertebral fractures has been reported in adult CF patients and this has been shown to inhibit airway clearance which can lead to a decline in lung function.
- Low bone mineral density is also considered a relative contraindication to transplantation.
- Approximately 50-75% of CF adults have low BMD & increased rates of fractures.

7.8.5 Monitoring of vitamin D levels

- The best clinical indicator of vitamin D status is 25-OHD. It gives a good measure of vitamin D stores and has a half life of 3-4 weeks.
- Biochemical evidence of vitamin D deficiency is frequently found in the absence of clinical symptoms so it is important that 25-OHD levels are measured regularly.
- It is reported that no consensus has yet been reached regarding the serum 25-OHD concentration required to optimise bone mineralisation in children, adolescents and young adults, with or without CF. A recent recommendation by the European cystic fibrosis guidelines however has suggested that to prevent vitamin D deficiency the recommended minimum 25-OHD concentration should be 50nmol/l.
- High dose vitamin D supplementation has recently been implemented within our trust which was based on the recently published European cystic fibrosis guidelines and on a recent observational assessment of our patients, which indicated a large proportion of our patients have inadequate vitamin D levels despite routine use of Vitamin D supplements. Please see CF Vitamin D guideline on the RBH Intranet.

- Vitamin D toxicity has not been reported however to avoid the risk of toxicity occurring with high dose vitamin D supplementation serum vitamin D levels are requested to be reviewed regularly when a patient is on high dose Vitamin D.

Vitamin preparations and recommendations

Preparation	A (IU)	D (IU)	E(mg)	K (mg)	Calcium (mg)
A+D Capsules	4000	400	0	0	0
Multivitamin Capsules BPC	2500	300	0	0	0
* Forceval Capsules	2500	400	10	0	60
* AquADEK	9,084	400	50	0	0
* ADEK	4000	400	100	0	0
Vita-E 200IU Gel Capsules	0	0	134	0	0
Vita-E 400IU Gel Capsules	0	0	268	0	0
Vitamin E Suspension/ml	0	0	100	0	0
Menadiol Sodium Phosphate	0	0	0	10	0
Colecalciferol capsules	0	50,000	0	0	0
Colecalciferol IM preparation	0	300,000	0	0	0
Calcichew D3 Caplets	0	400	0	0	

*** Not currently used within the Trust.**

- Routine supplementation for pancreatic insufficient patients and pancreatic sufficient with low fat soluble vitamin levels receive:
 - A+D capsules x2 daily
 - Vita-E Gel capsules 400IU x1 daily
 - Menadiol Sodium Phosphate 10mg daily
- Some alternative liquid solutions are available if required.
- Calcium and vitamin D supplements and high dose vitamin D supplementation are implemented as and when indicated.

7.9 CONSTIPATION AND DISTAL INTESTINAL OBSTRUCTIVE SYNDROME

It is thought that constipation and distal intestinal obstructive syndrome is more common in cystic fibrosis patients receiving sub optimal or excessively high doses of pancreatic enzyme therapy or when a rapid increase in enzyme dose occurs, however the incidence of distal intestinal obstructive syndrome varies widely and the pathophysiology is not fully understood.

Although DIOS is not fully understood there are often multiple contributory factors including:

- Dehydration
- Rapid increase in enzyme use
- Viscid intestinal secretions
- Altered gut motility and pH
- Poor compliance with enzyme therapy

Viscid muco-faeculent material accumulates in the terminal ileum / caecum leading to partial obstruction with pain usually in the lower quadrant, abdominal fullness and a palpable mass in the right iliac fossa. Patients often report having their bowels open as usual, or sometimes having diarrhoea (from over flow).

Differential diagnosis

- Constipation
- Appendicitis
- Intussusception
- Biliary tract or gall bladder disease
- Acute pancreatitis
- Urinary tract infection
- GI cancer

Investigations

- A plain abdominal x-ray (AXR) is usually all that is necessary to diagnose DLOS or constipation. However if there is still doubt over the cause of abdominal pain, the following may be helpful:
- WBC, amylase, liver function tests.
- Urinalysis
- Stool culture, stool microscopy for fat droplets, 3-day faecal fat.
- AXR - dilated small bowel loops with "bubbly" ileocaecal mass, classic feature but not commonly seen.
- Abdominal ultrasound.
- Barium /gastrografen enema - by specialist radiologist can diagnose and help treatment at same time.
- After the acute episode, consider faecal fat study.

Management

1. Chronic

- Check dose / compliance / timing of enzyme supplements.
- Diet – ensure adequate dietary roughage.
- Ensure adequate fluid intake.
- Laxatives may help e.g. lactulose 5-20 mls bd or movicol.
- If ongoing malabsorption is documented consider:-
 - Acid reduction with ranitidine or omeprazole

2. Acute

Gastrografen (oral) - 100 mls in 200 to 400 ml water or juice

- Patient must be **well hydrated** before, during and 3 hours post gastrografen, as it is highly osmotic. The suggested fluids above are the minimum.
- Repeat at 24 hours if no response

Rectal Gastrografen – 100 mls twice daily are also effective

Intestinal lavage with Kleen Prep a balanced electrolyte solution which can be administered either orally or via a nasogastric tube at a rate of 0.75 – 1 l/h to a total volume of 4-7 litres

- The aim is to take solution until clear fluid is passed PR.
- NG tube is usually required as volume is so large but occasionally some patients will prefer to drink it (more palatable if cool).

Colonoscopy with installation of gastrograffin

Colonoscopy is performed under sedation and gastrograffin 500 mls and 50% solution is instilled to the lumen at the site of obstruction. This is performed when other treatments have failed and in consultation with Dr Westaby. (NB: this prevents the need for laparotomy in most patients)

7.9.1 Constipation

Simple constipation should not be confused with DIOS related to fat malabsorption. It is important to recognise that increasing doses of pancreatic enzymes which may prevent DIOS can be counterproductive in constipation.

Treatment:

- Ensure adequate fluid intake.
- Lactulose 5-20 mls twice daily or Movicol may be used.
- Ensure dietary review re fibre intake.
- Chronic constipation refractory to the above measures should raise suspicions in older adults and referral to Dr Westaby and Dr Steele is recommended for CT +/- colonoscopy (note higher incidence of GI cancers in CF adults).

7.10 LIVER DISEASE

Reports of the prevalence of liver disease in CF vary but cirrhosis has been reported in 24% CF patients and up to 50% in post mortem findings. However, symptomatic liver disease is uncommon, being reported as the cause of death in only 2% of CF patients. Incidence does not rise progressively but seems to peak during the second decade and is more common in males (3:1). There is no known genotype-phenotype correlation but there is a high familial concordance and strong association with certain polymorphisms that may be predictive of future disease. There is a wide spectrum of hepatobiliary complications arising in CF patients. They include steatosis and focal or multilobular biliary cirrhosis. In infancy, presentation may be conjugated hyperbilirubinaemia secondary to bile duct obstruction (neonatal cholestasis) due to inspissated bile or with fatty change that may cause abdominal distension. Gallstones and cholecystitis can occur in CF adults.

Steatosis (Fatty liver)

This is a relatively common CF finding, occurring in 23-67% of patients. The pathogenesis is unclear, although it has been suggested that it arises secondary to fatty acid or carnitine deficiency, or insulin resistance. Its natural history is still uncertain and the frequency of progression to cirrhosis is unknown.

Detection of liver disease

There is no single gold standard for the diagnosis of liver disease, but careful attention should be given to the following:

- Palpation of an enlarged liver and/or spleen.
- Ultrasound.
- Liver function tests (transaminases) have a poor sensitivity and specificity. Consider drug causes – discuss with the pharmacy team at the earliest opportunity.
- Prolonged prothrombin time (although more likely to be due to malabsorption of vitamin K than liver disease).

Standard treatment

In patients with hepatomegaly, significantly elevated liver function tests, abnormal clotting or evidence of cirrhotic changes on liver USS:

- Ursodeoxycholic acid (increases bile flow). It is well tolerated with main side effect of diarrhoea, in which case reduce the dose. This reverses markers of CF liver disease but it is unclear whether it can delay or reverse fibrosis.
- Vitamin K (if prothrombin time prolonged) – If PTT corrects then continue with daily oral vitamin K. Occasionally IV stat doses are required.
- Avoid aspirin and NSAIDs in those with documented cirrhosis.
- Care with fusidic acid, minocycline, rifampicin, (If in doubt consult with BNF)
- Caution with itraconazole and voriconazole – See BNF

Referral to specialist pancreato-biliary CF service (Dr Westaby & Dr Steele)

Refer any adult CF patient with evidence of chronic liver disease for assessment

Investigations to facilitate specialist assessment should include up to date liver ultrasound, liver function tests, albumin and clotting studies in addition to viral studies to exclude other causes of liver disease.

Treatment of complications

- Patients with Cirrhosis and Portal Hypertension should be reviewed as a minimum twice per year in the specialist CF GI clinic and have endoscopy as directed by Dr Steele and Dr Westaby to assess for varices
- Variceal bleeding should be avoided by pre-emptive endoscopic banding
- Acute management of a variceal bleed should be under the care of the Hepatology team (as directed by Dr Westaby and Dr Steele)
- Liver transplant should be considered in patients with FEV1 50% or > who have suffered variceal bleeding. This is carefully discussed at the CF GI clinic.

7.11 GASTRO OESOPHAGEAL REFLUX

Gastro oesophageal reflux is common in adults with CF. The most common symptoms of gastro oesophageal reflux are heartburn and acid regurgitation but it can present without those symptoms but with deteriorating lung function and frequent exacerbations. Evaluation of the asymptomatic patient might require oesophageal pH and impedance studies.

Treatment – is with proton pump inhibitors. In addition prokinetic drugs such as Domperidone are useful NB: symptoms refractory to high dose proton pump inhibition or if associated with an abnormal haemoglobin should trigger referral to the GI clinic for further investigation and endoscopy (note - increased incidence of GI cancer in CF and early recognition of neoplasia is important).

8: CYSTIC FIBROSIS-RELATED DIABETES

8.1 BACKGROUND

All CF individuals with exocrine pancreatic insufficiency have insulin deficiency, which worsens with increasing age. Insulin secretion is reduced even in individuals with normal glucose tolerance. There is an increase with age in the prevalence of impaired glucose tolerance and diabetes.

The reported prevalence of CFRD depends on the diagnostic criteria used and screening methods, but approximately 50% of individuals with CF will have CFRD by 30 years of age. CFRD is NOT type II diabetes mellitus. In CF the insulin response to a glucose load or a meal is reduced in amplitude and delayed compared to normal individuals, but basal insulin secretion is relatively preserved. The typical pattern in the early stages is for fasting glucose to be normal with elevated glucose levels after meals.

Why we treat CF-related diabetes and impaired glucose tolerance

The prevalence of diabetes rises as age of survival increases. Cystic fibrosis related diabetes is a distinct type of diabetes which has features of both Type 1 and Type 2 diabetes. CFRD reduces life expectancy so it is critically important to diagnose early. The development of cystic fibrosis related diabetes is associated with worse lung function and poorer nutritional status in comparison with non-diabetic cystic fibrosis patients. Individuals with CF who have diabetes or impaired glucose tolerance have worse outcomes (lung function, nutritional status, reduced survival) compared with those with normal glucose tolerance. There is evidence that treating the insulin deficiency associated with CF can improve this.

The adverse impact of insulin deficiency is probably associated with loss of the anabolic effect of insulin; loss of nutrition related to glycosuria and possibly increased infection risk with elevated glucose. Risk of microvascular complications in diabetes increases with worse control and duration of diabetes, and appears to be the same in CF as in other forms of diabetes.

8.2 ASSESSMENT AND SCREENING

Oral glucose tolerance tests are used to screen for diabetes during every patients' annual assessment. The oral glucose tolerance test is currently the most specific and sensitive tool to diagnose cystic fibrosis related diabetes. This test is also useful when a patient is clinically stable and has a history of raised HbA1c, weight loss and/or deteriorating lung function.

Serial glucose monitoring is also a specific and sensitive tool to aid diagnosis of cystic fibrosis related diabetes. This usually follows an impaired or diabetic oral glucose tolerance test. Patients are usually encouraged to keep a food diary in conjunction with blood glucose monitoring to ascertain the relationship between diet and blood glucose. The diary is also a useful tool for the dietitian to assess and analyse how best to optimise dietary intake and hence nutritional status. The patient can also gain knowledge and awareness by self completing a food and blood glucose diary.

Fasting and random glucose levels and HbA1c measurements each serve a purpose however lack sensitivity and specificity in cystic fibrosis because patients with cystic fibrosis can have transient elevation of random and fasting glucose measurements without having a diabetic oral glucose tolerance test (the opposite situation can also occur). Random and fasting glucose tests are usually performed during a patients' hospital

admission. They support diagnoses of cystic fibrosis related diabetes alongside the oral glucose tolerance test and monitoring of serial blood glucose levels.

It is important to remember that even oral glucose tolerance test results will vary according to a patient's nutritional status, infection and liver dysfunction however oral glucose tests and serial blood glucose monitoring remain the most sensitive tool for diagnosing cystic fibrosis related diabetes.

Treatment for patients should be considered and commenced in those with a diabetic oral glucose tolerance test and/or regular hyperglycaemia and anyone with an impaired oral glucose tolerance test with associated weight loss, high blood glucose levels or deteriorating clinical condition.

Insulin remains the treatment of choice although a minority of patients may be able to achieve control with oral tablets (Repaglinide). A referral to the Diabetologist at Chelsea and Westminster Hospital or to the Royal Brompton's monthly cystic fibrosis related diabetes clinic should be made for all patients diagnosed with cystic fibrosis related diabetes.

8.2.1 When to test for glucose status in CF

- Current CF Trust recommendation is for OGTT once yearly in all adult CF patients without CFRD.
- Clinical concerns- poor weight gain, decline in lung function with no other obvious cause.
- All patients admitted with an exacerbation should have skin prick testing of blood sugars as a screening test for the first 48 hours of admission
- Finding of high random glucoses in any individual (most normal individuals can maintain their glucose <7.8 mmol/l). Formal assessment is required if there are repeated glucose levels >8.0 mmol/l or a single level >11.0 mmol/l.
- Abnormal HbA1c on annual review, ie level >6.5%.
- Symptoms of hyperglycaemia, including increased thirst, polyuria, blurred vision, constipation and candida infections.
- Consider testing before high dose steroids, starting overnight feeds, or before major surgery.
- Consider testing if there are documented hypoglycaemic episodes or symptoms suggesting this.
- Women planning to get pregnant who haven't had an OGTT in the previous six months should be screened for CFRD.
- Pregnant women should have an OGTT as soon as possible following confirmation of pregnancy and subsequently at least between weeks 24 and 28 of term.

8.2.2 Oral glucose tolerance test

Glucose levels are measured before and after a standard oral glucose load.

Preparation

- The patient is fasted from midnight although drinks of water are allowed.

Dose of glucose

- A standard 75g of glucose as Polycal® liquid 113mL diluted in water (200-300 mL).
- A glucose drink giving the same dose of glucose can be substituted, such as Lucozade. The glucose content varies with the type but is clearly printed on the label, so calculate a volume to give the equivalent amount of glucose. Lucozade Energy "original" contains 17.2g glucose/100ml and the dose of this is 10.2 ml/kg to a maximum of 436 mls.

Samples

- Take venous blood sample for glucose at 0 mins (fasting) and give the glucose drink.

- Take second venous blood sample for glucose at 120 minutes.
- Pregnant women should also have a sample taken at 60 minutes post glucose load.

Advantages of OGTT

- Easy to carry out and only takes 2 hours.
- Most individuals with abnormal glucose tolerance will have an abnormal OGTT.

Disadvantages

- The cut off values for diabetes and impaired glucose tolerance are based on risk for cardiovascular disease in type 2 diabetes and do not apply to CF where the aims of treatment are different. For individuals developing type 2 diabetes an OGTT is a clear guide to when to treat (when the test indicates a diagnosis of diabetes) but in CF because individuals with impaired glucose tolerance get benefit from treatment OGTT is not a clear guide as to when to treat.
- OGTT will miss a significant number of individuals with abnormal glucose tolerance in CF, particularly if only baseline and 120 minute tests are done.

When to use

- As an easy screening test if there is suspicion based on clinical status.
- OGTT is not needed if the diagnosis of diabetes is already established with CGMS or random glucose levels.

Standard WHO criteria for the diagnosis of diabetes and impaired glucose tolerance	
Definition	Clinical features
Diabetes	Symptoms plus random glucose concentration ≥ 11.1 mmol/l or Fasting glucose of ≥ 7.0 mmol/l or 2 hour plasma glucose over ≥ 11.1 mmol/l after OGTT
Impaired glucose tolerance	Fasting plasma glucose < 7.0 mmol/l, and 2 hour plasma glucose ≥ 7.8 mmol/l to < 11.1 mmol/l after OGTT
Impaired fasting glucose	Fasting glucose of ≥ 6.1 mmol/l to < 7.0 mmol/l

Profile of random glucose tests

Checking random glucose levels over a few weeks can give a good picture of glucose status. Draw up a clear plan of how many tests are needed (ideally 3 or 4 a day) and when to do them. The common practice in type 1 diabetes is to test pre meal; in CF testing should be before and also 1-2 hours after meals. The most likely time for glucose to be high is about 2 hours after the evening meal.

Advantages

- Easy to arrange as an outpatient.
- Most people tolerate this well.

Disadvantages

- Choice of time to test can mean that you do not get a clear picture, accidentally or deliberately.

8.2.3 HbA1c

- This is not of value as a screening test but high or climbing HbA1c is an indication to more formal testing.

8.2.4 CGMS

- Continuous Glucose Monitoring System (CGMS) gives the most comprehensive picture of glucose status and is helpful in guiding treatment. If this is not available a profile of random glucose levels or OGTT should be done. Random glucose levels can be helpful in deciding insulin regimen.
- A subcutaneous sensor gives a profile of glucose levels for up to 6 days. The plastic sensor reads glucose in the interstitial fluid every 5 minutes. The sensor needs to be calibrated with blood glucose measurements four times daily for as long as the probe is in place, and the profile can be downloaded at the end of the study. The equipment gives a profile and statistical breakdown of the glucose levels.

Advantages -

- CGMS gives a better picture of glucose status in CF than either OGTT or random glucoses and also frequently shows glucose peaks that would not otherwise be detected.
- The effect of food, exercise and treatment on glucose levels can be assessed.
- It may be a better guide as to when to start insulin treatment in CF but data are limited.

Disadvantages -

- The sensor is sometimes uncomfortable and some individuals cannot tolerate it.
- Blood glucose still needs to be measured 4-6 times in 24 hour period which can be a problem with needle anxiety.
- Clear guidelines as to when to treat on the basis of CGMS are not available.
- The sensors are relatively expensive (£35-44 each).

When to use -

- CGMS is the best test to use to decide on the need for treatment if there are high random glucose measurements (over 7.8 mmol/l) or clinical concern (poor weight gain, decline in lung function with no other obvious cause).
- CGMS can guide choice of insulin regimen (see below).
- It can give information on control for individuals already on insulin (for example whether overnight feeds are adequately covered).

8.3 TREATMENT OF DIABETES AND ABNORMAL GLUCOSE TOLERANCE IN CF

The primary cause of the abnormal glucose tolerance in CF is insulin deficiency so the treatment for this is insulin. Insulin has been shown to improve lung function and nutritional status in CF; whereas studies with oral hypoglycaemic agents suggest that while they can control glucose levels in some individuals, there is no sustained benefit to clinical state, so we rarely use them.

Who should be treated?

- Everyone with a diagnosis of diabetes as defined above unless there are overwhelming clinical or psychological reasons preventing this.
- Everyone with symptomatic hyperglycaemia.
- Consider treatment if there is abnormal glucose tolerance, not confirming a diagnosis of diabetes but:
 - Declining lung function or nutritional status with no other cause found.
 - Nutritional concerns, for example on overnight feeds or supplements and not gaining weight.
- CGMS shows that glucose levels are frequently high (over 7.8mmol/l). A recent study has shown declining lung function when glucose was over 7.8 mmol/l for over 4.8% of the day.

What insulin to start

These decisions are not made by the respiratory team alone but in conjunction with the CF diabetes team and the specialist dietitians. The idea is to use short acting (such as Novorapid) and long acting (Levemir) insulin to try to cover the glucose levels and meals best. Many individuals with CF can manage on one type of insulin, either mealtime Novorapid or once daily Levemir, at least at first. Many young adults with CF have erratic eating habits and flexibility is important, so avoid a regimen which means they have to eat to avoid hypoglycaemia. When starting insulin, look at the pattern of glucose on profile and CGMS:

- Normal fasting glucose but elevated glucose just after main meals
 - Start Novorapid before meals.
- Normal fasting glucose with elevated glucoses during the day but no fixed pattern after meals
 - Start Levemir before breakfast.
- Elevated fasting glucose and high glucoses through the day
 - Start Levemir before breakfast, adjust this dose and then add in Novorapid with meals.
- Overnight feed with glucoses rising during the night
 - Start Levemir given 1-2 hours before the feed starts. Novorapid may be needed during the day as well to cover meals.
- On steroid treatment
 - Start Levemir given in the morning and adjust, this is the best way to cover the rise in glucose in the afternoon after oral steroids in the morning. If the glucose levels are very high with steroid treatment, a useful strategy is to give Levemir morning and evening and then adjust independently.
- No pattern or very erratic eating habits
 - Start Levemir given in the morning and adjust then add in Novorapid if needed.

Starting doses of insulin

- Levemir- use 2-8 units depending on weight of the individual
- Novorapid – use 2-4 units to cover meals. The insulin dose depends on the carbohydrate content of the meal and so a larger dose is needed for a larger meal.
- Much larger doses may be needed for individuals on high dose steroids.

Adjusting insulin doses after starting

- Ideally only change one thing at a time.
- Go up by 1 unit at a time for Novorapid and 2 units at a time for Levemir or Glargine.
- The effect of a change in long acting insulin may take several days to be clear.
- You occasionally need to increase in larger steps for a patient on steroids with rising glucoses.
- Try to increase the long acting insulin first and then the short acting.

What to adjust

- Adjust the meal time dose on the basis of the glucose after meals and the long acting insulin on the morning pre-breakfast glucose.
- Remember that the insulin you are giving is to control the glucose levels after it is given, not to try to correct what has already happened. Adjust the dose of insulin on the basis of the glucose level measured after it, not the glucose level before it.
- Short acting insulin given before the meal is to cover the meal and not to try to correct the glucose level before the meal.
- Remember the time course of the insulin- Novorapid lasts 2-4 hours, Levemir 16-20 hours and Glargine up to 24 hours.

Psychology referral is suggested as this is a stressful time for the patient with added treatment burden and possibly needle issues.

8.4 DIETARY ADVICE FOR CYSTIC FIBROSIS RELATED DIABETES

The primary aim of nutritional management in cystic fibrosis related diabetes is to achieve and maintain optimal nutritional status and glycaemic control and to prevent hyperglycaemia, hypoglycaemia and the acute and long term risks associated with poor diabetic control.

Managing cystic fibrosis related diabetes as a co-existing condition should not interfere with the achievement of a good nutritional status.

Following diagnosis patients receive individualised dietary advice from an experienced cystic fibrosis dietitian. The dietary recommendations for people with diabetes mellitus and those with cystic fibrosis are conflicting. Conflicts between dietary therapy of cystic fibrosis and diabetes should usually be resolved in favour of the cystic fibrosis diet.

Dietary restriction to control blood glucose levels is not advocated in cystic fibrosis as appropriate nutrition is critical to maintain body mass and lung function. Blood glucose should be controlled by adjusting insulin therapy to the requirements of adequate food intake and not by calorie restriction. Insulin is tailored to the patients' diet; the diet is not tailored to the patients' insulin.

The energy needs of cystic fibrosis patients whether they are diabetic or not is 120-150% of that required by health individuals of the same age, sex and size and it is important to consider that requirements increase with deteriorating clinical condition. The promotion of high energy food is necessary if patients are to meet their energy requirements which are in contrast to the dietary recommendations for non cystic fibrosis diabetes diet where the promotion of a low fat, low energy diet is usually encouraged.

To achieve a high energy diet and reduce post prandial peaks in glucose three main meals and at least three snacks are recommended. This can be difficult for patients to achieve. It is usually unnecessary to dramatically alter the eating patterns of patients who already have an established adequate oral intake. Smaller meals taken often can reduce the risk of hyperglycaemia and hypoglycaemia if patients have poor appetites.

A high fat diet which provides approximately 35-40% of energy as fat is encouraged for patients with cystic fibrosis related diabetes. A high fat diet may allow for a more moderate use of refined carbohydrates. Fat also slows the absorption of glucose from the intestine which prevents rapid rises in blood glucose levels. All varieties of fat are encouraged to ensure a plentiful supply of essential fatty acids.

Carbohydrate should provide 45-50% of the diets total energy intake. Many cystic fibrosis patients heavily rely on refined carbohydrates as a major source of energy. In the non cystic fibrosis patients diet refined carbohydrates should not exceed 10% of the total energy intake, however restricting the intake of refined sugary foodstuffs in a cystic fibrosis patients diet can have a serious detrimental effect on their total energy intake and nutritional status so refined carbohydrates are not routinely restricted. Patients are encouraged to balance the amount, type and timing of carbohydrate alongside hypoglycaemic medication, insulin therapy and activity levels.

Soluble fibre delays the rate of post prandial glucose absorption. A high fibre diet in cystic fibrosis patients with cystic fibrosis related diabetes can further compromise their nutritional status by reducing energy intake. A moderate increase in fibre intake for patients who are well nourished is appropriate.

Patients with cystic fibrosis related diabetes have been found to have an increase in protein metabolism. Uncontrolled hyperglycaemia has been shown to increase protein breakdown this results in catabolism of body protein stores. A diet which contains approximately 20% protein as energy intake should be advocated.

Alcohol suppresses gluconeogenesis and so has a hypoglycaemic effect. For patients' taking insulin, alcohol can cause hypoglycaemia with severe effects. Patients with cystic fibrosis related-diabetes should understand the effects of alcohol on their blood glucose levels. Alcohol can initially increase blood glucose levels due to the carbohydrate content of the alcoholic beverage however may make the blood glucose fall rapidly later. Patients should be encouraged to drink alcohol within safe limits, never drink on an empty stomach and consume a carbohydrate containing snack before bedtime.

If a patient requires nutritional supplements to optimise nutritional status then they should be incorporated into the diet in a regulated manner as indicated by a specialist cystic fibrosis dietitian. Milk or fat based supplements are preferred if possible and insulin should be adjusted accordingly.

Knowledge and success with the practical management of insulin administration and adjustment, glucose monitoring and hypoglycaemia, exercise and illness are extremely important if a patient is to achieve good glycaemic control and prevent cystic fibrosis related diabetes affecting overall clinical status. It is important that the cystic fibrosis multidisciplinary team work together to help the patient achieve this.

Hypoglycaemia

- Hypoglycaemia is a blood glucose less than 4.0 mmol/L and any glucose lower than this should be treated even if the patient feels well.
- Symptoms of hypoglycaemia include confusion, irritability, pallor, fatigue, dizziness, and a "wobbly" or "funny" feeling, and most patients can easily identify if they have low blood glucose.
- Hypoglycaemia can be caused by a number of factors- too much or wrongly timed insulin dose, insufficient carbohydrate intake, exercise, missed enzyme doses, diarrhoea and vomiting leading to poor absorption of food, alcohol consumption.

Treatment of hypoglycaemia

Give a rapidly-absorbed carbohydrate followed by a complex-carbohydrate snack. There is an understandable tendency to over treat hypoglycaemia, which can result in hyperglycaemia later on. Chocolate and sweets are not a good alternative for the initial treatment of hypoglycaemia- they are not as rapidly absorbed as glucose, and it gives the wrong psychological message to reward hypoglycaemic episodes. If the test before a dose of insulin shows hypoglycaemia, treat the hypoglycaemia and then go ahead with the meal and give the normal insulin.

- If hypoglycaemia is suspected test the blood glucose if possible.
- Treat hypoglycaemia with 10g of rapidly absorbed carbohydrate (50 ml of Lucozade, 100 ml of coca-cola, 3 glucose tablets, 2 tsp. of jam/honey/syrup).
- Wait 15 minutes and test blood sugars again. If < 4.0 mmol/L, repeat step 2. If > 4.0 mmol/L, give a complex-carbohydrate snack (such as a sandwich, crisps or 3-4 biscuits).
- Think about what caused the hypoglycaemia.

Diabetic ketoacidosis (DKA)

DKA is virtually unknown in CFRD but remember in some young adults with a family history may have Type 1 diabetes. DKA should be managed according to national consensus guidelines (see NHS Diabetes).

8.5 ENTERAL FEEDING AND CYSTIC FIBROSIS RELATED DIABETES

Any patient being considered for enteral feeding should have an oral glucose tolerance test performed to exclude undiagnosed cystic fibrosis related diabetes as a cause of their poor nutrition. Even in patients who have recently undergone an oral glucose tolerance test with normal results, monitoring of blood glucose pre- and post-feed and once during the feed should be routine practice to assess effects of enteral tube feeding on nocturnal glycaemia. Some patients do develop nocturnal hyperglycaemia and may require insulin to cover their overnight feed only.

Patients with established cystic fibrosis related diabetes will require close monitoring and adjustment of insulin therapy during the introduction of enteral feeding. There is not a specific enteral feed for cystic fibrosis related diabetes.

A sliding scale insulin or insulin infusion should be titrated against 4-6 hourly blood glucose levels for patients receiving parenteral nutrition.

Cystic fibrosis related diabetes can be precipitated by steroid therapy or respiratory exacerbation in patients with glucose intolerance so insulin therapy and dietary/enteral feed adjustment may be applicable for a short period of time only.

8.6 PRACTICAL ASPECTS TO CONSIDER

Equipment

Ideally patients should go home with spares of pens and glucose meters. Remember to contact the GP to make sure that supplies of insulin, pen needles, lancets and strips for the meter are added to the regular prescription. Pharmacy at RBH does not keep glucose meters. Most patients will need 6-8mm needles for their pens. Never use needle and syringe for insulin and always use an appropriate device for pricking fingers.

Outpatient follow up

Royal Brompton Hospital - Nicola Bridges and Kevin Shotliff come to the Adult CFRD Clinic on the last Thursday morning of each month.

Monitoring

A realistic plan for monitoring blood glucose levels at home should be discussed. HbA1c should be checked every 3-4 months. Individuals with CFRD are at increased risk of neuropathies and nephropathy therefore eye screening and checks for microalbuminuria should be done yearly.

Other practical aspects

- We advise patients to consider who they should inform that they have diabetes, as family members, partners, friends, college or work colleagues may have to assist a patient during a hypoglycaemic episode.
- If a patient with diabetes is travelling abroad they need a letter saying that they are travelling with insulin, needles and glucose testing equipment (this can be added to the letter about their CF).

- There are strict rules covering driving and diabetes. Patients applying for a licence must declare their diabetes and must get medical confirmation that they are well controlled.
- Prior to any general anaesthetic a plan must be made to reduce the insulin while the patient is fasting. Make sure anaesthetists are informed in advance.

Useful links:

The CF Trust: <http://www.cftrust.org.uk/aboutcf/publications/factsheets/Factsheet - Diabetes-for web %28Sept 2010%29.pdf>

The CF Trust: <http://www.cftrust.org.uk/aboutcf/publications/consensusdoc/diabetes.pdf>

Diabetes UK: <http://www.diabetes.org.uk/>

9: OTHER ISSUES

9.1 TRANSPLANT ASSESSMENT

9.1.1 Discussion of transplant assessment

Discussion regarding transplantation should be led by a consultant who knows the adult with CF well. This is best discussed at an annual review outpatient review but changes in clinical state may mandate that this discussion occurs during an admission or soon afterwards. Issues of transplantation should not be raised by the junior members of the team in the first instance.

9.1.2 Referral

Lung transplant assessments are usually carried out at Harefield Hospital, occasionally, when a patient is very sick the assessment may be carried out on Foulis ward. A referral proforma has to be completed and sent to Dr Martin Carby with a referral letter from a consultant. The referral proforma requests information including:

- Patient demographic data
- Family and social history
- Respiratory history: microbiology, oxygen use, smoking history, thoracic surgery, NIV, exercise capacity, rate of decline.
- Full past medical history
- Current medication including adherence to treatment
- Psychological assessment
- Clinical investigations: weight, height, ECG, echocardiogram, chest x-ray, HRCT thorax, arterial blood gas, DEXA, GORD testing, full lung function, blood tests (plus group and cross match)

9.1.3 Nutritional concerns and transplantation

Poor nutritional status has been shown to compromise post transplant survival and increases the risk of post operative complications. Nutritional status should be optimised prior to and during the time of transplant assessment. To be eligible for transplant body mass index usually needs to be no less than 17kg/m^2 however optimising nutritional status by achieving a body mass index between $20\text{--}25\text{kg/m}^2$ has been shown to result in better outcomes post transplant.

9.2 BONES

CF adults are at risk of low bone mineral density. Bone health is optimised by ensuring adequate vitamin D levels. In adult males low testosterone levels can also contribute and may require correction. The use of steroids is associated with loss of bone density therefore patients receiving chronic steroid therapy should be monitored carefully.

All patients should have DEXA scanning on transition to the adult clinic and a plan formulated for regular DEXA scans depending on the results. (This will be directed by Dr Stephenson and reported on the DEXA scan report).

The use of bisphosphonates should be considered in patients with documented subnormal bone mineral density, ie Z score less than -1.5 who are starting prolonged steroid therapy or who are being assessed for lung transplantation. Dr Stephenson will advise in other situations.

Bisphosphonates cross the placenta and women of child bearing age who wish to become pregnant should be fully informed of potential risks to the foetus if pregnancy occurs. Even if bisphosphonates have been discontinued prior to conception there is a theoretical risk that they could be released from bone during pregnancy and harm the foetus.

In summary, prevention of low bone mineral density is the best approach.

9.3 ENT

9.3.1 Nasal polyps

- May occur in up to 40% of adults with CF.
- Aetiology is uncertain but may be related to infection, allergy, immune factors, altered secretions and abnormal cilia. There is also an association with chronic sinus infection.
- Usually asymptomatic.
- Can result in chronic nasal obstruction which increases airway resistance and may lead to mouth-breathing and obstructive sleep apnoea syndrome.
- Can also cause headaches and impair smell and taste.
- Chronic rhinitis develops which can increase the incidence of pulmonary infections.

Diagnosis is made by simply looking up the nose with a light but sometimes it is difficult to differentiate them from inflamed turbinates.

If troublesome:

- Initial treatment is usually a steroid nasal spray such as fluticasone (Flixonase) or mometasone (Nasonex)..
- Anti-histamines are of no value.
- If unsuccessful, surgery should be considered, but due to the high recurrence rate (60-90%), multiple procedures may be necessary.
- Oral steroids are occasionally used for severe multiple recurrent polyps.

9.3.2 Sinusitis

- Although almost all patients with CF have chronic paranasal sinusitis, fewer are symptomatic.
- X-ray of the sinuses is of little value, as over 92% of all patients with CF will have opacification of the maxillary, ethmoid and sphenoid sinuses. Initially, opacity is due to retention of thick secretions but later it may be due to polyposis within the sinuses. The frontal sinuses rarely develop in children with CF, probably due to early onset of sinusitis, which prevents pneumatization. If referral to ENT is contemplated a CT scan will be helpful.
- Chronic sinusitis is commonly associated with nasal polyposis.
- Sinusitis may cause headaches, particularly on tilting the head forwards. Other symptoms are related to chronic nasal obstruction (mouth-breathing, snoring, loss of sense of smell and taste) and purulent drainage (postnasal drip, cacosmia – foul smells in the nose, constant throat-clearing, halitosis).
- Adults should be referred to the ENT clinic (Mr Saleh and Prof Durham) if they are suffering from difficult sinus symptoms.

9.6 ARTHROPATHY AND VASCULITIS

9.6.1 Arthropathy

The mean age of arthropathy onset is 13-20 years (depending on the series). Cystic fibrosis arthropathy (CFA) is a specific condition, which may be immune-complex mediated and related to chronic pulmonary infection and inflammation. Typically, patients have an episodic arthritis with pain and swelling, usually of large joints such as knees and ankles and wrists. It is often accompanied by low-grade fever and there may be erythema nodosum or an erythematous rash or purpura. Joint x-rays are usually normal. Episodes tend to settle spontaneously after 3-4 days and respond well to non-steroidal anti-inflammatory drugs (e.g. ibuprofen). Intensification of chest therapy may also help control joint symptoms. Beware renal toxicity when using IV aminoglycosides in those on regular ibuprofen.

Some patients with arthritis and advanced lung disease have features of hypertrophic pulmonary osteoarthropathy (HPOA), this occurs in 2-7% of CF patients with a median age of onset of 20 years. In this condition, as well as arthritis, which is often accompanied by joint effusions, there are features of periostitis. The latter consists of tenderness and pain over the long bones with periosteal elevation on x-ray. Periosteal changes may also be noted on radioisotope bone scan. HPOA is seen in patients with more severe lung disease and worsens during chest exacerbations. Anti-inflammatory drugs may be necessary.

Occasionally, sero-positive rheumatoid arthritis occurs in CF. It may require treatment with anti-inflammatory agents, steroids and regular infusions of immunoglobulin. Finally, it must be remembered that ciprofloxacin can cause arthropathy in both children and adults with CF. Onset of symptoms may occur between three weeks and two months but tend to respond within two weeks once the drug is stopped.

Dr Alex Brand, Consultant Rheumatologist at Chelsea and Westminster Hospital reviews any of our adults with recurrent symptoms.

9.6.2 Vasculitis

Cutaneous vasculitis presents as a petechial or maculopapular rash commonly involving the lower limbs. It is non-blanching, sometimes palpable, painful and can be itchy. Other symptoms include fever, malaise and myalgia. This can be recurrent and episodic in association with chest exacerbations. Treatment for cutaneous vasculitis without systemic involvement can be with non-steroidal anti-inflammatory agents but steroids and azathioprine may be required.

For patients experiencing more than a single transient episode we recommend assessment in the dermatological clinic with Dr Morar

10: FERTILITY, CONTRACEPTION AND PREGNANCY

10.1 CONTRACEPTION (MEN)

Almost all men with CF are infertile because of bilateral absence of the Vas Deferens. All adolescent males are told about infertility before transitioning to adult care; however, the adult CF team must not assume that they necessarily remember all the details. Although it should be assumed that all males are infertile this is not inevitable, contraception must be strongly encouraged including advice about 'safe sex', and condoms are therefore recommended. Male patients often confuse infertility with impotence so it is important to stress that they are not the same and that sexual performance is unaffected (although the volume of ejaculate may be reduced). If patients want to confirm infertility then they should be advised to ask their GP for a sperm test, this should not be done during a chest infection and two samples should be sent a couple of weeks apart.

As they get older many men with CF are keen to start families and there is information on microsurgical epididymal sperm aspiration and intracytoplasmic sperm injection (ICSI) available from the CF nurses. Planning a family should involve early discussion with the CF team, and should include optimising health before the procedure and before birth, maintaining treatment regimens once the baby is at home, and issues of child care and support as one parent becomes ill and eventually dies.

http://www.infertilitynetworkuk.com/uploadedFiles/Resources/Factsheet_storage/Cystic%20Fibrosis%20and%20Infertility%20in%20Men.doc

10.2 CONTRACEPTION (WOMEN)

Women are not infertile, so again contraception must be encouraged; the only way to be protected from sexually transmitted infections is to use a condom. Useful information on the types of contraception is available from various sources including the Family Planning Association, or the NHS Choices website; however patients should be encouraged to either seek advice from their GP or from a Family Planning Clinic.

There are 15 different methods of contraception available to women:

- Methods that are used every time: Male and female condoms. Diaphragm or cap.
- Methods that are taken every day: Pill (the combined pill or the progestogen-only pill).
- Methods that are replaced every week: Contraceptive patch.
- Methods that are replaced every month: Vaginal ring.
- Methods that are renewed every three months: Contraceptive injection.
- Methods that are renewed up to every three years: Contraceptive implant.
- Methods that are renewed up to every five years: Intrauterine device (IUD).
Intrauterine system (IUS).

A useful website for women trying to work out which different contraceptive method would be best for them is: www.fpa.org.uk/helpandadvice/mycontraceptiontool

The only types of antibiotic that interact with hormonal contraception making it less effective are rifampicin and rifabutin as these are enzyme-inducing. Enzyme-inducing antibiotics speed up the processing of some contraceptive hormones and therefore reduce the levels in the blood making the contraceptive less effective. If these drugs are going to be taken patients should be advised to change their contraception to a different method.

Contraception methods affected by rifampicin or rifabutin include:

- The combined pill
- The progestogen-only pill
- The implant - Nexplanon (Implanon was discontinued in 10/10, but some women will still have them in-situ)
- The patch
- The vaginal ring

Contraception methods that are not affected by rifampicin or rifabutin include:

- The progestogen injection - Depo-Provera
- The intrauterine device (IUD)
- Intrauterine systems (IUS)

10.2.1 Emergency contraception

There are two types of emergency contraception:

- The emergency contraceptive pill (Levonelle One Step, or Levonelle 1500). In addition there is a new emergency contraceptive pill available, the 'ellaOne'. It can be taken up to five days (120 hours) after sex and is only available on prescription.
- The IUD (intrauterine device), which is more effective for emergency contraception.

When giving advice over the phone women can be told that they can obtain both types of contraception free from a GP surgery that provides contraception, a contraceptive clinic, a sexual health clinic, some genitourinary medicine (GUM) clinics, and some young people's clinics (*call 0800 567123*). The emergency contraceptive pill can also be provided free from some pharmacies, most NHS walk-in centres and minor injuries units, and some Accident and Emergency departments. Levonelle One Step can be bought from most pharmacies if patients are 16 years or over, the cost varies, but is currently about £26.

How does emergency contraception work?

- Levonelle One Step, or Levonelle 1500 has to be taken within 72 hours of unprotected sex. It is more effective the sooner it is taken. It contains progestogen, and works by delaying or preventing ovulation.
- The IUD can be inserted into the uterus up to five days after unprotected sex, or up to five days after the earliest time following ovulation.

How effective is emergency contraception?

If taken within 24 hours of unprotected sex, Levonelle One Step, or Levonelle 1500 will prevent 95% of pregnancies that could be expected if no emergency contraception were used. Eighty-five per cent of pregnancies are prevented if the pill is taken between 25 and 48 hours after unprotected sex, and up to 58% of pregnancies if taken 49-72 hours after unprotected sex. The sooner it is taken, the more effective it will be. The IUD will prevent 99% of pregnancies, and in addition can be used as an ongoing contraceptive method.

What to advise patients after emergency contraception

- The emergency contraceptive pill may cause nausea, dizziness, headaches, tender breasts or abdominal pain.
- The next period may be earlier or later than usual.
- There can be some discomfort when the IUD is put in analgesia should be made available. If the IUD is used then it can continue as an ongoing method of contraception.

10.3 PREGNANCY

Encouraging young women with CF to feel confident in discussing their reproductive plans with the CF team is an important step in planning a safe and successful pregnancy. Women with poorer health status must have the problems of conception and the risks of becoming pregnant clearly pointed out to them, although assuring that care and support will continue whatever their decision they make.

Planning a pregnancy takes time and effort. Genotyping the partner and genetic counselling should take place as early as possible. Prenatal testing should be available (CVS or amniocentesis). Liaison with obstetric colleagues is essential and coordination of appointments helpful, especially as the pregnancy progresses. Good communication between the obstetric and CF teams throughout the pregnancy ensures that the mother's health remains stable.

Health should be optimised and usual care adopted when planning a pregnancy eg starting folic acid, liaison with GP. Regular outpatient attendance must be encouraged and where possible homecare support should be provided, particularly in the latter stages of the pregnancy.

The realities of CF must be discussed with the couple. They will need to consider where they will get both ongoing practical and psychological support, the implications of being a one parent family, financial support and planning for the child's future. Women who are in employment will need to think about reducing their hours during the pregnancy and early discussion with employers helps this transition.

As with the general population some women with CF may not be able to conceive. There are options available, although not all are available to everyone. These include intrauterine insemination (IUI), in vitro fertilisation (IVF), adoption, fostering or (rarely) surrogacy. A referral to an assisted conception unit may be made, however the links with the CF and obstetric teams must be maintained.

10.2.1 Guidelines for management

1. Genotype partner, this can be done by the partners GP or at a Genetic Testing Laboratory where counselling is also provided.
 - Blood should be sent in a 10 ml EDTA bottle.
 - Nationality, ethnicity, and family history of CF should be included on the request form (including any known mutations).
 - State on request form that the partner has CF and the couple are trying to conceive.
2. Antenatal screening: The couple should be referred for genetic counselling to help them decide whether they would like antenatal screening (CVS, which can be performed around 10-12 weeks gestation or amniocentesis which is usually slightly later). Because of the approximately 1% chance of miscarriage, this is thought by most to be appropriate only for those parents who are considering termination of an affected foetus.

On the basis of the limited number of mutations screened for, some CF patients will be, for example, F508/N, meaning one detected and one undetected allele. Failure to detect both mutations in the proband does not rule out the possibility of antenatal or sibling diagnosis, as linkage analysis based on Restriction Fragment Length Polymorphisms (RFLP) may be possible. Parental blood samples are required.

3. Pre-implantation diagnosis: For patients wishing to consider pre-implantation diagnosis, to ensure an unaffected foetus, we usually ask their GP to refer them to Professor Peter Braude at Guy's Hospital. There may be an issue with PCTs agreeing to pay for the procedure. Referral forms are downloaded from www.pgd.org.uk and sent to -

Nurse Consultant (PGD/Genetics)
Clinical Genetics
7th Floor, Borough Wing
Guy's Hospital
Great Maze Pond
London SE1 9RT

Tel: 0207 188 1364
Email: pgd@kcl.ac.uk

4. Refer the patient to an experienced obstetrician (we refer to Mr Guy Thorpe-Beeston, Consultant Obstetrician/Gynaecologist at Chelsea & Westminster Hospital - 0208 746 8000).
 - Refer for an early meeting with the obstetrician to discuss pregnancy, options and plan of care.
 - Ensure close liaison and communication links between the CF and obstetric teams.
 - If the Chelsea & Westminster Hospital is not chosen for delivery then the hospital of choice must have access to Intensive Care and Neonatal Units.
5. Maintaining clinical care
 - Review current medication list as some drugs will need to be stopped.
<http://www.ecfs.eu/files/webfm/webfiles/File/documents/Pregnancy.pdf>
 - Attention to nutrition (see below).
 - Attention to airway clearance.
 - CF outpatient appointments to coordinate with obstetric outpatients, frequency of visits will increase during pregnancy.
 - Monitoring for gestational diabetes (usually by the obstetric team).
 - CF Homecare/telephone clinic support.
 - Admissions – especially before the planned date of delivery.
6. Psychosocial care
 - Discuss the possible deterioration of health status during pregnancy, encourage early recognition of the need for treatment and admissions.
 - Identifying sources of ongoing support (practical and psychological) post delivery e.g. parents, friends, nurseries / crèches / other childcare – does the baby need to be registered at a nursery before birth?
5. Post pregnancy
 - Aim to regain pre-pregnancy health status.
 - Warn mothers about emotional and physical exhaustion.
 - Increasing treatment demands / admissions versus baby care. Prepare parents that caring for their baby may have priority over treatment; however this must not be neglected, they may need to find help.

The CF team can support the new mother during this time by careful planning of outpatient appointments, providing CF Homecare, email or telephone access. Often the partner or family will also need support and referral to the local midwife or health visitor can provide other sources of assistance.

10.2.2 Nutritional concerns and pregnancy

As survival of patients with cystic fibrosis increases more women with cystic fibrosis wish to become pregnant.

It is well known that women who are well nourished and who have good lung function preconception and during pregnancy will generally have a better pregnancy outcome than women with a poor nutritional status and lower lung function. It is well documented that low pre-conception body mass index is associated with a high risk of low birth weight babies.

Pre-conception

- Nutritional assessment during pre-conception prepares the patient. This assessment aims to identify key areas that may need special attention.
- Optimising maternal health and fertility and preventing the risk of neural tube defects is the priority at this stage of care. This involves assessing the patient's nutritional state and providing advice to optimise oral intake with particular attention given to high energy, protein, calcium and vitamin D rich foods. Daily folic acid supplementation of 400mcg should be recommended till the 12th week of pregnancy and advice on food safety, alcohol, fish, caffeine and food borne illnesses is also warranted at the pre-conception stage.
- Women with cystic fibrosis with good lung function and healthy body mass index (20-25kg/m²) should have no issues with the ability to conceive. Patients with suboptimal nutritional status can have a reduced ability to conceive.
- Though unusual, cystic fibrosis patients who are overweight may also suffer with reduced fertility and may be at increased risk of developing gestational diabetes which can lead to a compromised nutritional status and increased risk of complications during pregnancy.
- Women who plan their pregnancies and have pre-conception advice have significantly greater maternal weight gain and heavier babies.

Nutritional management during pregnancy

- Patients are closely monitored during pregnancy with particular emphasis on nutrition and weight gain.
- The average energy cost of pregnancy is estimated at approximately 80,000 calories. The recommended energy requirements for pregnancy are approximately 200-300 calories per day in the last trimester only. Patients with a low body mass index pre-conception or uncontrolled malabsorption due to pancreatic insufficiency are however likely to need more energy than this to support adequate weight gain for pregnancy.
- In normal pregnancy weight gain varies widely but generally 12.5kg is considered the average weight gain. In cystic fibrosis weight gain is significantly less than that of healthy women. An increase in weight of at least 10kg has been associated with a good outcome. Target weight gain is to achieve at least 10kg during the pregnancy; with targets of 0.5kg per week from 20 weeks gestation.
- Weight gain should be monitored on a regular basis as frequent as every 4-6 weeks as poor appetite, nausea and vomiting, gastro-oesophageal reflux, altered gastric motility, constipation, diabetes, poor lung function and pulmonary complications can be difficult to manage during pregnancy and can easily compromise weight gain and nutritional status.
- Women with cystic fibrosis clearly require additional nutritional support during pregnancy. If they are unable to achieve this via diet alone, then nutritional supplements and furthermore enteral feeding may be advocated as a suitable option to ensure the mother and baby's health is not compromised. Invasive nutritional support measures should be considered early in pregnancy when it is best tolerated.
- Various methods of enteral feeding can be considered during pregnancy however short term options via nasogastric tube feeding is usually first line treatment when oral nutritional support measures have failed. Gastrostomy feeding however can be considered as alternative option if deemed appropriate. Pregnant

- Enteral feeds are best tolerated when given as a continuous pump rather than as a bolus particularly during the later stages of pregnancy when intragastric pressure increases due to uterine enlargement. The introduction of enteral tube feeding should be closely monitored to assess if it affects blood glucose levels. Parenteral feeding should be considered if enteral nutrition has been insufficient to promote adequate weight gain. This is usually reserved for extreme cases where the risks and benefits have been considered carefully.

Vitamins and minerals during pregnancy

- Both severe vitamin A deficiency and excess are teratogenic and associated with adverse reproductive outcomes. Supplementary doses of vitamin A in excess of 10,000 IU or 3000 µg per day have been associated with increased incidences of birth defects in infants during pregnancy.
- Serum vitamin A levels are monitored closely pre-conceptionally and during pregnancy. If levels of vitamin A are high then vitamin A supplementation is reduced. If levels of vitamin A are low or normal vitamin A supplementation is continued at a level less than 10,000 IU daily and serum vitamin A levels monitored closely. Additionally foods with high vitamin A content should not be eaten excessively as they too can cause hypervitaminosis A.
- Iron deficiency is common in cystic fibrosis. Cystic fibrosis women may enter pregnancy with inadequate stores and even healthy cystic fibrosis women may find it difficult to meet the metabolic demands of pregnancy. To prevent iron deficiency patients should be encouraged to increase their intake of dietary iron and vitamin C which will help optimise absorption of iron. Tannins and other foods which reduce the bioavailability of iron should be restricted.
- Iron levels should be monitored regularly and supplementation considered if deficiency is developing.

Diabetes and pregnancy

- Diabetes has been associated with poorer prognosis whether diagnosed pre-pregnancy or as gestational diabetes.
- Complications of pregnancy are more common in women with cystic fibrosis related diabetes and gestational diabetes. The most frequent complication is pre-term delivery. Lung function was also found to be lower in women who deliver pre-term.
- Raised blood glucose levels in the first trimester are associated with an increased risk of teratogenesis. During the second and third trimester raised blood glucose levels are associated with an increased risk to both mother and fetus.
- Women with cystic fibrosis who are already at risk of cystic fibrosis related diabetes are at high risk of gestational diabetes.
- Prior to conception patients with impaired glucose tolerance must have their blood glucose levels monitored closely and treatment initiated if necessary. The preferred form of treatment is insulin. Short acting insulin can be taken after meals if nausea and vomiting make oral intake unpredictable. Oral intake is not restricted and a high energy diet is encouraged. Insulin therapy is adjusted according to the patient's food intake.
- Women with established diabetes must optimise diabetes control prior to conception to reduce the risk of complications and patients with normal glucose tolerance should have an oral glucose tolerance test carried out in each trimester.
- Referral should be made to the specialist Diabetic/Obstetric team at Chelsea and Westminster hospital for any patients with known impaired glucose tolerance or established cystic fibrosis related diabetes prior to conception and those with impaired oral glucose tolerance at presentation.

Lactation

Breast feeding and breast milk have considerable benefits for both the infant and the mother however the mothers preferred feeding method should always be respected. There is no contraindication for a mother with cystic fibrosis to breastfeed provided an adequate energy intake can be maintained as breast feeding has an energy cost of approximately 500 calories per day.

11: SOCIAL AND EDUCATIONAL ISSUES

11.1 WELFARE RIGHTS

The adult CF service has the support of a Welfare Rights Adviser who gives advice on issues such as benefits, housing and employment. It is always a good idea to check to see if patients are entitled to claim benefits especially if there has been a change to health. It is also a good idea to provide patients with advice when claiming.

11.1.2 Benefits Advice

The Welfare Rights Adviser provides advice and assistance with all welfare benefits, including working benefits, sickness benefits, disability benefits, income related benefits, housing and council tax benefits and benefits for students. Additionally the Welfare Rights Advisor will also provide help with benefit appeals.

In recent years common reasons for contact include advice and support around housing issues, financial support while at college and the Employment and Support Allowance (ESA) and Work Capability Assessment. This is often when existing sickness benefits such as Income Support and Incapacity Benefit are being changed over to ESA.

11.1.3 Housing Advice

The Welfare Rights Adviser provides advice and assistance with housing applications, re-housing and homelessness working closely with the medical and psychological teams in order to provide the supporting evidence that will assist decision making on housing and benefit claims. This ensures that claims include the specific information needed and minimises the number of tribunals and the stress that otherwise can often occur.

11.2 EDUCATIONAL SUPPORT

The Role of the Hospital School on Foulis Ward

Around the age of 16 years patients at the Royal Brompton Hospital transition from the paediatric medical team on Rose ward (as well as other paediatric wards from other hospitals) to the adult team on Foulis ward for their care.

The Hospital School team on Foulis is a small group of highly experienced staff led by the school's Principal. The team includes Teachers, Artists, Careers advisor, Therapist and ICT expert who have expertise and in depth knowledge in their relevant fields and the curriculum. The Hospital School is a continuing presence on Foulis ward after leaving the paediatric setting. Many of the young adults on Foulis ward continue with their studies into Higher and Further education and the school team are able to provide continuity and much valued educational support for them during their admissions whilst inpatients to Foulis ward.

For those young adults who are no longer in education we offer information about courses, alternative pathways for post 16 education, advice on volunteering opportunities and possible entitlements. The teaching team also work with young adults to help initiate and develop their own projects. Whilst an inpatient on Foulis Ward post 16 pupils have one-to-one sessions with teachers, who can liaise with and work collaboratively

with their tutors at college and university to ensure continuity of educational provision. This service is invaluable at a time the young person can feel quite isolated.

The young people on Foulis ward also have access to a careers advisor who can support them with education and careers advice, guidance for CV writing and supporting statements as well as interview practice.

The school is open 50 weeks of the year shutting for only two weeks over the festive period. During Holiday times the school runs an organised Arts and ICT programme. The school is a registered exam centre ensuring that patients are able to sit exams even if they are in Hospital.

Education

If you have any queries about school or college work please speak to the teachers who can offer support to patients. If patients need resources the school can provide textbooks and multimedia resources which can be borrowed whilst they are on the ward. Teachers are able to liaise with colleges or educational institutions and obtain the relevant work. The teachers also provide lessons in many of the subject areas which are delivered by the highly qualified team of teachers in most of the subjects areas.

Examinations

If patients are on Foulis Ward at the time of an external examination, they will have the option to sit exams on the ward as Foulis ward is a registered examination centre and is common practice on the ward. Many young people in the Hospital school are keen to sit exams in the subjects that they have worked very hard towards. In most cases they have been working towards these exams for a long time and anxieties can arise at the thought of not being able to sit that all important examination. This can be arranged very quickly via our examination officer, as long as the young person and the medical team are happy for this to go ahead. Everything will be put in place to ensure that they have the opportunity to continue with this part of their education.

Arts

Shaun Dolan is the artist in residence at Chelsea Community Hospital School. He can support exam projects in Art & Design, help individuals to develop their own creative ideas or involve them in ward art projects on Foulis. There are many examples of the wonderful work that Shaun and the young people do in and round the Hospital. Shaun leads individual and collaborative projects throughout the year.

Reflexology

Sarah Hurley is a qualified reflexologist and offers reflexology to patients on Foulis Ward. Reflexology can be deeply relaxing, helping patients to de-stress and ease anxiety. Some patients find that during a treatment their breathing becomes more regular. The tightness in their chest relaxes, making it easier for them to cough. Some patients have also found reflexology helpful for abdominal problems. Likewise students working towards exams find it a wonderful way to unwind from the stresses and strains of the examination period.

ICT

ICT support is available on Foulis to help with computer troubleshooting. This support is on a weekly basis. There is also support with website design and ICT related projects. A ward blog has also been created allowing patients with CF to sign up and exchange ideas, pictures and videos.

Outings/ Visits to places of Interest

Members of the school team offer short trips and visits to local places of interests and also facilitate visits the local library for a quiet place to study.

MDT Meetings

The school team meet every month with the ward as part of the 'School Involvement Team'. This meeting is used as an opportunity to share the work that the team does with the young people with the wider CF MDT team on Foulis. The school also works closely with the transition team to ensure a smooth transition from paediatrics to the adult ward.

11.3 TRAVELLING

Young people with CF are keen to make the most of every opportunity for a more adventurous day-to-day life, with increased choice of potential holiday destinations and activities; however, anyone planning a holiday should be encouraged to discuss travel plans with the CF Team.

Places to avoid

Over recent years, there have been several cases of Melioidosis. This is an infection caused by *Burkholderia pseudomallei* and can be potentially life threatening. *Burkholderia pseudomallei* can be found in fresh water and damp soil in some areas of Asia and Northern Australia. Patients should also be aware of the potential risks of going to countries where hygiene standards and medical care are poor.

Preparation

Fit to Fly Tests - If patients have an FEV₁ of <50% or oxygen saturations of <95% they should be advised to have a fitness to fly test which will identify if oxygen is required on a flight. Patients should have repeated tests before each trip as their oxygen requirements may change.

Oxygen, nebulisers and compressors - Each airline has its own policy on oxygen transport and in-flight usage. Patients should contact their airline before they book in order to find out their policy. The airline will need to know whether oxygen is required during the entire flight or intermittently. Some airlines will provide oxygen free of charge or for a small fee. The airline will then request a MEDIF form which will need to be completed by a doctor from the CF Team stating the patient's oxygen requirements and that they are fit to travel.

Some low-cost airlines do not supply oxygen themselves but they will allow patients to take their own approved oxygen supply on board, commonly portable oxygen concentrators. Portable oxygen concentrators are fairly new but are increasingly being allowed on more flights. They are lightweight and can run on electricity or battery. They are not widely available yet however patients maybe able to borrow one from RBH so please discuss with the clinical nurse specialists. They are available to purchase but bear in mind they remain an expensive piece of equipment.

If patients require oxygen at their destination, the patient should get in contact with their UK oxygen supplier who should be able to arrange this as well as during stop-overs if necessary.

Medication - Patients are advised to pack a separate set of medication in their hand luggage as well as in their suitcase in case their luggage goes missing. If medicines need to be refrigerated, patients can be advised to carry a cool bag or vacuum flask on board. Any equipment that will be needed during the flight should be battery powered as there will be no electrical supply available on board. Most airlines will not allow the use of nebulisers during take off or landing. If patients need to carry out treatment/medication during the flight they should inform the airline.

Power, pumps and plugs - Power supply varies from country to country. UK electrical appliances such as nebulisers may not work in certain countries. The physiotherapy department maybe able to offer a travel compressor and patients should purchase electrical adapters due to different plug sockets.

Paperwork - When travelling abroad patients should carry a letter from their CF Team outlining all of the medicines and equipment that they will need to travel with (including needles, syringes, compressors). Travel insurance is essential and should be encouraged. It is essential that their insurance covers “pre-existing” conditions. This may mean that insurance cover is more expensive but otherwise they will not be covered for CF-related treatment.

When travelling in the EU patients can apply for a European Health Insurance Card (EHIC). This entitles them to either free treatment or treatment at a reduced cost if they fall ill when travelling in Europe. It will also cover treatment for chronic or pre-existing conditions. However this should not be a substitute for travel insurance as it only covers emergency care and does not include some medication costs and repatriation.

Documentation required for patients to travel:

- Fitness to fly letter from doctor
- A letter detailing current medical condition and medication and equipment
- Travel insurance certificate
- EHIC if travelling in EU

Optimising health

Some patients may require a course of IV antibiotics before they travel to optimize their health. The CF team need to know travel dates in advance so that a plan for admission can be made, however admission priority will always be for patients who are unwell and need treatment. Every effort is made to accommodate pre-holiday treatment but admission dates have to be flexible. Additionally, patients may need to consider back-up oral antibiotics to take with them.

There may be circumstances that patients are advised not to travel such as recent haemoptysis, recent pneumothorax, gastrointestinal obstruction or acute chest infections. These will be discussed with the consultants at the time, travel plans may need to be postponed or cancelled.

Risk of salt depletion - Heat can cause excessive sweating, which can lead to dehydration, Slo-Sodium (4-6 daily) is recommended. Patients travelling to hot countries and those who will be engaged in strenuous sports or other activities (eg cycling and skiing) must be prescribed enough for the duration of the holiday and advised to stay well hydrated (particularly when drinking alcohol).

Vaccinations and immunisations – Patients should be advised to visit their GP as soon as possible to check if they need any vaccinations or other preventive measures (such as malaria tablets). Remember, these treatments are not usually available as NHS prescriptions.

General travel health advice

Sometimes general health issues can be forgotten when planning travel, therefore patients must be reminded to use a high-factor sunscreen and avoid excessive sunbathing especially if they are on certain oral medication (eg voriconazole, ciprofloxacin). Patients also need to be reminded to practice safe sex; they should be advised to take condoms with them as quality varies in different countries.

12: END OF LIFE CARE

12.1 THE SPECIALIST PALLIATIVE CARE TEAM

Specialist palliative care at The Royal Brompton Hospital is provided by The Royal Marsden and Royal Brompton Palliative Care Service. The team comprises 1 WTE Consultant in Palliative Medicine and 1 WTE Clinical Nurse Specialist supported by a larger palliative care team based at The Royal Marsden NHS Foundation Trust and the wider multidisciplinary team based at The Royal Brompton.

The service provides face-to-face consultations Monday-Friday 9am-5pm and telephone advice from the on-call Consultant Palliative Medicine (accessed via the switchboard of The Royal Marsden NHS Foundation Trust) during the out-of-hours periods.

The Specialist palliative care team (PCT) is a multi-professional team providing an advisory service to patients and staff. It is designed to complement the hospital services by providing evidence-based, individualised, symptom control, complex psychosocial care, liaison with other specialist palliative care services (hospital and community) and terminal care for all patients with advanced disease. The PCT is committed to audit, research, education and providing a service that provides quality of life, patient choice and treats patients and their carers with respect and dignity at all times.

12.2 COMPLEX SYMPTOM CONTROL

Guidelines for symptom control can be found on The Royal Brompton and Harefield NHS Foundation Trust Intranet. The contents of the booklet outline the current practice of the PCT and concentrate on pharmacological strategies for symptom control. It should be noted that they have been written for health care professionals based at The Royal Marsden NHS Foundation Trust and may not necessarily apply to units outside of this cancer centre.

Whilst many of the strategies for symptom control identified in the guidelines are likely to be transferrable to the patient with a diagnosis of Cystic Fibrosis, a close working relationship between the PCT and the CF team is imperative. Of particular note is the high incidence of side effects witnessed following the use of metoclopramide in the management of nausea and vomiting in the patient with CF. This experience has led the team to avoid the use of metoclopramide where possible.

12.3 END OF LIFE CARE

The PCT provides support to patients approaching the end of life. Support is also provided for their carers and staff and where possible can involve advance care planning promoting patient-centred care aimed at maximising patient autonomy and choice.

The Liverpool Care Pathway for the Dying Patient is available on the CF ward at The Royal Brompton Hospital. This is an integrated care pathway recommended as a best practice model by the Department of Health used at the bedside to ensure the quality of care for patients in the last days of life is optimal.

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13.1: Oral Antibiotics

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Chloramphenicol	<p><u>Treatment</u> 12.5 – 25 mg/kg QDS. Usually 500 mg QDS; maximum 1g QDS.</p> <p>May be prescribed at higher dose initially and reduced to lower dose as soon as clinically indicated, e.g. 1g QDS for 24-48h, reducing to 500mg QDS thereafter</p>	<p><i>H. influenza</i>; Anecdotal reports of a clinical response in patients with <i>P.aeruginosa</i> and <i>B.cepacia</i> complex.</p> <p>The patient should be fully informed of the risks of chloramphenicol: blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia), peripheral neuritis and optic neuritis. There are no reported cases of aplastic anaemia in a CF patient but this does not warrant complacency.</p> <p>Needs full blood count at day 21 if course longer than 3 weeks. Courses not normally repeated within 3 months.</p>	<p>Hepatic effects Avoid if possible in hepatic impairment. If not possible, reduced dose may be required to maintain trough level <10mg/L.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min Dose as in normal renal function</p> <p>Manufacturers recommend monitoring levels in patients with renal impairment. Therapeutic range: peak = 10-20 mg/L; trough = 5-10 mg/L</p>	<p>Pregnancy Not associated with increased incidence of congenital malformations. Concerns that use near term may be associated with a risk of neonatal Gray Baby Syndrome are not supported by evidence.</p> <p>Lactation An alternate drug is preferred to chloramphenicol during breastfeeding, especially while nursing a newborn or preterm infant. If the mother must receive chloramphenicol during nursing, monitor the infant for gastrointestinal disturbances and adequacy of nursing. Monitoring of the infant's complete blood count and differential is advisable. In some cases, discontinuation of breastfeeding might be preferred.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ciprofloxacin	<u>Treatment</u> 750mg BD	<p><i>P. aeruginosa</i></p> <p>Included in RBH NTM protocol</p> <p>Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping. Quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use; patients over 60 years of age are more prone to tendon damage; the risk of tendon damage is increased by the concomitant use of corticosteroids; if tendinitis is suspected, the quinolone should be discontinued immediately.</p> <p>Patients should be reminded about photosensitivity - avoid exposure to sunlight or UV radiation and use high factor sun block during and for up to 4 weeks post treatment.</p> <p>Dairy products will reduce absorption. Avoid for at least 30 min. before and after taking ciprofloxacin.</p> <p>May lower seizure threshold - use with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued.</p>	<p>Hepatic effects</p> <p>No dose adjustments necessary in hepatic impairment.</p> <p>Renal Impairment</p> <p>GFR 20-50mL/min Dose as in normal renal function</p> <p>GFR 10-20mL/min Dose as in normal renal function</p> <p>GFR <10mL/min Reduce to 50% of normal dose (100% of dose may be used for short periods in exceptional circumstances – seek advice from a pharmacist).</p>	<p>Pregnancy</p> <p>Limited evidence does not suggest any increased risk of adverse pregnancy outcomes.</p> <p>Lactation</p> <p>Fluoroquinolones have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, recent studies indicate little risk. The calcium in milk might prevent absorption of the small amounts of fluoroquinolones in milk, but insufficient data exist to prove or disprove this.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Clarithromycin	<u>Treatment</u> 500 mg BD Extended release 1000mg OD may be required in some circumstances.	<i>S. aureus</i> ; <i>H. influenzae</i> ; mycoplasma Included in RBH NTM protocol. Interacts with some drugs metabolised by CYP450 isoenzyme system – may increase plasma concentrations of drugs such as theophylline, ciclosporin, tacrolimus, simvastatin, warfarin. Contact pharmacist for further advice.	Hepatic effects Use with caution in hepatic impairment. Renal Impairment GFR >30mL/min Dose as in normal renal function GFR <30mL/min 250-500mg BD (<10mL/min, vomiting may be a problem with higher doses). Avoid extended release preparations in severe renal impairment.	Pregnancy Exposure to clarithromycin during pregnancy has not been associated with teratogenic effects. Lactation Because of the low levels of clarithromycin in breast milk and administration directly to infants, it is acceptable in nursing mothers. The small amounts in milk are unlikely to cause adverse effects in the infant. Monitor the infant for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis.
Co-amoxiclav (amoxicillin + clavulanic acid)	<u>Treatment</u> 625 mg TDS	<i>S. aureus</i> ; <i>H. influenzae</i> (β -lactamase positive); <i>Moraxella catarrhalis</i> Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. The risk of acute liver toxicity is reported to be about 6 times greater with co-amoxiclav than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men. Jaundice is usually self-limiting and very rarely fatal.	Hepatic effects Use with caution and monitor liver function at regular intervals (use with caution in CF liver disease). Due to clavulanic acid content duration should not exceed 14 days without review. Contra-indicated if patient has previous history of jaundice/hepatic dysfunction which may be penicillin associated. Renal impairment (all levels) Dose as in normal renal function.	Pregnancy No conclusive evidence of an increased risk of congenital malformations or foetal loss following maternal exposure to therapeutic doses. Lactation Amoxicillin and clavulanic acid is acceptable to use during breastfeeding. Limited information indicates that serious reactions in infants are very uncommon during the use of amoxicillin-clavulanic acid during nursing.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Co-trimoxazole (sulfamethoxazole and trimethoprim)	<u>Treatment</u> 960 mg BD	Used mainly for <i>S. maltophilia</i> . Also active against <i>S. aureus</i> , <i>H. influenzae</i> and may be useful for <i>B. cepacia</i> . Included in RBH NTM protocol	Hepatic effects No data are available relating to dosage in patients with impaired hepatic function. Contra-indicated in patients showing marked liver parenchymal damage. Renal Impairment GFR 30-50mL/min Dose as in normal renal function GFR <30mL/min 50% of normal dose	Pregnancy Avoid in pregnancy: Potential increased risk of hyperbilirubinaemia in neonates with other risk factors. Lactation With healthy, full-term infants it appears acceptable to use sulfamethoxazole and trimethoprim during breastfeeding after the newborn period.
	<u>Prophylaxis</u> 960 mg BD	Associated with rare but serious side effects: Stevens-Johnson syndrome, bone marrow suppression and agranulocytosis. Monitor FBC in prolonged courses. Advise patient to report sore throats and fevers. Stop if rash or blood disorder develops.		

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Doxycycline	<u>Treatment</u> 200mg on first day then 100-200 mg OD	Can be useful for <i>S maltophilia</i> and <i>B cepacia</i> , and MRSA. Also active against most <i>H. influenzae</i> and some <i>S. aureus</i> Included in RBH NTM protocol	Hepatic effects Avoid or use with caution in patients with hepatic impairment or those receiving potentially hepatotoxic drugs. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Use in pregnancy is associated with perturbed fetal bone growth, congenital cataracts and discolouration of teeth in the child and may exacerbate fatty liver of pregnancy in the mother. Tetracyclines should be avoided after the first trimester unless compellingly indicated. Lactation There is not likely to be harm in short-term use of doxycycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breastmilk. Short-term use of doxycycline is acceptable in nursing mothers. As a theoretical precaution, avoid prolonged or repeat courses during nursing. Monitor the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhea or candidiasis
	<u>Prophylaxis</u> 100mg daily	Advise patients to swallow caps/tabs whole, with plenty of water and in an upright position to avoid oesophageal irritation. Headaches and visual disturbances need investigating (benign intracranial hypertension reported with tetracyclines). Discontinue if blood disorders develop. Patients should be reminded about photosensitivity - avoid exposure to sunlight or UV radiation and use high factor sun block during and for up to 4 weeks post treatment.		

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ethambutol	<u>Treatment</u> 15mg/kg (maximum 1.5g) OD (round dose to nearest 100mg)	Included in RBH NTM protocol – <i>M.avium</i> complex. Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. Test visual acuity with Snellen chart, and colour vision with Ishiharhi colour vision test before treatment and warn patient to report visual changes.	Hepatic effects No dose adjustment required in hepatic impairment Renal Impairment GFR 10-50mL/min Dose as in normal renal function GFR <10mL/min 15mg/kg every 48h or 7.5mg/kg/day	Pregnancy The literature supports the safety of ethambutol during pregnancy. Lactation Limited information indicates that maternal doses of ethambutol up to 15 mg/kg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months.
Flucloxacillin	<u>Treatment</u> 1 – 2g QDS <u>Prophylaxis</u> 1g BD (can increase to 2g BD)	<i>S. aureus</i> Patients should be advised to take 1 hour before meals or on an empty stomach as far as practical. Review at discharge whether to resume on prophylactic dose. Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors.	Hepatic effects Cholestatic jaundice, hepatitis and reversible changes in LFT's are rare and may occur up to 2 months after treatment has been stopped (more common following prolonged therapy). Contraindicated in patients who have a history of flucloxacillin associated hepatic dysfunction or jaundice. Use with caution in patients with hepatic dysfunction. In prolonged treatments regular monitoring of hepatic function is recommended. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Considerable clinical experience has not indicated adverse foetal effects when flucloxacillin is used in pregnancy. Lactation Penicillins and cephalosporins are the antibiotics of choice during breastfeeding. However, trace quantities of flucloxacillin can be detected in breast milk: the possibility of hypersensitivity reactions must be considered in breast-feeding infants.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Fusidic acid/ sodium fusidate	<u>Treatment</u> sodium fusidate tabs 500mg TDS; fusidic acid liquid 750mg TDS (Doses may be doubled in severe infection) NB Doses of fusidic acid are higher than sodium fusidate due to differences in bioavailability (fusidic acid is incompletely absorbed). Fusidic acid 375 mg \equiv sodium fusidate 250 mg.	<i>S. aureus</i> Patients should be advised to take with or after food Should always be prescribed with additional anti-staphylococcal agent to prevent resistance.	Hepatic effects Periodic LFTs recommended if on high dose, prolonged therapy or in patients with liver dysfunction. Caution when taken with other antibiotics with similar biliary excretion pathways (rifampicin). It displaces bilirubin from its albumin binding site <i>in vitro</i> . The clinical significance of this finding is uncertain. Drug elimination may be decreased in hepatic impairment, biliary disease and biliary obstruction; avoid or reduce dose. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Inadequate evidence of safety in human pregnancy. Lactation Safety in nursing mothers has not been established. When sodium fusidate has been given systemically, levels have been detected in the breast milk. Caution is therefore required when used in mothers who wish to breast feed.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Linezolid	<u>Treatment</u> 600 mg BD	<p>Last line for MRSA or <i>S aureus</i> where patients have not responded to conventional agents e.g. high dose flucloxacillin, rifampicin, fusidic acid.</p> <p>Courses >28 days (consultant decision only) leads to risk of optic neuropathy. Patients should be warned to immediately report any visual changes, regardless of treatment duration. Patients expected to need >28 day course or repeated courses should have ophthalmic exam before starting first course and every 2 months after.</p> <p>Haematopoietic disorders reported – full blood counts should be monitored weekly. Close monitoring needed if treatment for more than 10–14 days, pre-existing myelosuppression, severe renal impairment or receiving any drugs that may affect haemoglobin, blood counts or platelet function.</p> <p>Linezolid is a reversible monoamine oxidase inhibitor and therefore should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B, or within two weeks of taking any such medicinal product.</p>	<p>Hepatic effects</p> <p>No dose adjustment is required in hepatic impairment, however, in severe hepatic impairment use only if potential benefit outweighs risk.</p> <p>Renal Impairment (all levels) Dose as in normal renal function. Monitor closely if GFR <10mL/min: if platelet count drops on dose of 600mg BD, consider reducing to OD.</p>	<p>Pregnancy</p> <p>No reports of use during human pregnancy: use alternatives if possible. If no other alternatives are available and linezolid must be used, the maternal benefit appears to outweigh the unknown foetal risk.</p> <p>Lactation</p> <p>If linezolid is required by the mother, it is not a reason to discontinue breastfeeding. Monitor the infant for possible effects on the gastrointestinal tract, such as diarrhoea, vomiting, and candidiasis. However, because there is no published experience with linezolid during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Metronidazole	<u>Treatment</u> 400 mg TDS	<p>most anaerobic protozoa; Gram-negative anaerobes</p> <p>Remind patients to avoid alcohol for duration of therapy. May darken urine.</p> <p>Do not use suspension in patients taking ranitidine or PPIs due to limited absorption – if tablets cannot be swallowed whole, crush and disperse in water.</p>	<p>Hepatic effects</p> <p>Significant accumulation may occur in patients with hepatic encephalopathy resulting in high plasma concentrations which may contribute to the symptoms of the encephalopathy - use with caution. In severe liver disease reduce total daily dose to one third (give once daily). AST may be spuriously low while on metronidazole. Regular monitoring required if duration of treatment >10 days.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>Manufacturer advises against a single high dose regimen during pregnancy. Available data does not indicate an increased risk of congenital malformations or adverse foetal effects associated with use in pregnancy.</p> <p>Lactation</p> <p>Hold breastfeeding during treatment with metronidazole.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Minocycline	<u>Treatment</u> 100mg BD	Can be useful for <i>S. maltophilia</i> , <i>B. cepacia</i> , <i>A. xylosoxidans</i>	Hepatic effects If patients develop signs or symptoms of hepatotoxicity, minocycline should be discontinued. If treatment continues for >6 months, monitor every 3 months for hepatotoxicity. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Use in pregnancy is associated with perturbed fetal bone growth, congenital cataracts and discolouration of teeth in the child and may exacerbate fatty liver of pregnancy in the mother. Tetracyclines should be avoided after the first trimester unless compellingly indicated. Lactation There is not likely to be harm in short-term use of minocycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breastmilk. Short-term use of minocycline is acceptable in nursing mothers. As a theoretical precaution, avoid prolonged or repeat courses during nursing. Monitor the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhoea or candidiasis. Black discolouration of breastmilk has been reported with minocycline
	<u>Prophylaxis</u> 100mg OD – BD	Included in RBH NTM protocol. Advise patients to swallow caps/tabs whole, with plenty of water and in an upright position to avoid oesophageal irritation. Headaches and visual disturbances need investigating (benign intracranial hypertension reported with tetracyclines).		

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Moxifloxacin	<u>Treatment</u> 400mg OD	<p>Included in RBH NTM protocol.</p> <p>Not active against <i>P. aeruginosa</i> or MRSA</p> <p>Has been associated with QT interval prolongation therefore contra-indicated in: Congenital or documented acquired QT prolongation; Electrolyte disturbances, particularly in uncorrected hypokalaemia; Clinically relevant bradycardia; Clinically relevant heart failure with reduced left-ventricular ejection fraction; Previous history of symptomatic arrhythmias. The manufacturer advises that moxifloxacin should not be used concurrently with other drugs that prolong the QT interval: risks and benefits must be considered if this is deemed necessary. Other general advice on quinolones including effect on seizure threshold, photosensitivity and tendon damage also applies – see under ‘ciprofloxacin.’</p>	<p>Hepatic effects</p> <p>Has been associated with life-threatening hepatotoxicity. Use is contraindicated in severe liver impairment and those with 5 x increase in transaminases. Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests should be carried out in cases where possible liver dysfunction has occurred.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>No reports of moxifloxacin in pregnancy. Evidence of toxicity in animals would suggest that it should be avoided.</p> <p>Lactation</p> <p>Short-term use of moxifloxacin is acceptable in nursing mothers. However, it is preferable to use an alternate drug for which safety information is available.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Rifampicin	<p><u>Treatment</u> <50kg: 450mg BD >50kg: 600mg BD</p> <p>In <i>Mycobacterium avium</i> complex (MAC) infection, rifampicin is administered OD (600mg)</p>	<p>Second line for <i>S aureus</i>. Usually given with fusidic acid.</p> <p>May be useful as an adjunct in biofilm-associated infections.</p> <p>Included in RBH NTM protocol</p> <p>Advise patients to take at least 30 minutes before, or 2 h after food; stains body secretions red/brown.</p> <p>Rifampicin is a potent inducer of certain cytochrome P-450 enzymes. Co-administration with other drugs that are also metabolised through this system may accelerate the metabolism and reduce the activity of the other drugs. Caution should therefore be applied when prescribing rifampicin with other drugs, notably azoles, prednisolone, caspofungin, warfarin, antiepileptics, oral contraceptives, clarithromycin, immunosuppressants, simvastatin. This list is not exhaustive – if in doubt as to effects on other drugs, discuss with pharmacist.</p>	<p>Hepatic effects</p> <p>Take baseline LFT's and monitor for hepatotoxicity. Contraindicated if the patient has jaundice. In liver dysfunction including CF liver disease, do not exceed 8mg/kg/day and ensure careful monitoring of liver function - especially serum alanine transaminase (ALT) and serum aspartate transaminase (AST) which should initially be carried out prior to therapy, weekly for two weeks, then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn.</p> <p>Renal Impairment GFR 10-50mL/min Dose as in normal renal function GFR <10mL/min 50% to 100% of normal dose</p>	<p>Pregnancy</p> <p>Few published studies do not indicate an increase in risk of congenital malformations.</p> <p>Neonatal haemorrhage has been reported following exposure to rifampicin in late pregnancy: maternal supplementation with vitamin K is recommended when rifampicin is administered during the last few weeks of pregnancy.</p> <p>Due to the reports of low birth weight in infants of women being treated with rifampicin, monitoring of fetal growth may be warranted.</p> <p>Lactation</p> <p>Excreted into breast milk in small amounts which are thought to represent a low risk to the nursing infant – no adverse effects in nursing infants have been reported.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Trimethoprim	<u>Treatment</u> 200 mg BD	<p>May be useful for <i>B. cepacia</i> complex and MRSA in combination with other antibiotics.</p> <p>May cause depression of haematopoiesis, particularly when given over prolonged periods or in high doses.</p> <p>Monitor blood counts and advise the patient to report sore throats, fevers, and mouth ulcers, bruising or bleeding.</p>	<p>Hepatic effects</p> <p>Use with caution in patients with severe hepatic damage as changes may occur in the absorption and metabolism of trimethoprim.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>No overall increased risk of congenital malformation has been demonstrated with trimethoprim use in human pregnancy, although an increased risk of neural tube defects, cleft lip/palate and cardiac defects has been reported.</p> <p>Folate supplementation may reduce risks: high dose (5mg) folic acid is recommended in all women treated with trimethoprim during the first trimester as a precautionary measure.</p> <p>Lactation</p> <p>No reports found regarding neonatal toxicity following exposure to trimethoprim during lactation.</p>

13.2: Intravenous antibiotics

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Amikacin	OD dosing (Non NTM) 15mg/kg once daily (Maximum 1500mg OD)	<i>Pseudomonas aeruginosa</i> (OD dosing)	OD dosing All doses, in 100mL sodium chloride 0.9% over 30 minutes	OD dosing Trough must be <5mg/L Hepatic effects No precautions necessary Renal Impairment GFR 20-50mL/min dose as in normal renal function GFR < 20mL/min 12mg/kg OD, adjusted according to trough level	Pregnancy No reports of congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. However, eighth cranial nerve toxicity in 2nd and 3 rd trimester in human foetus after exposure to other aminoglycosides is well known and amikacin could potentially cause this. Close monitoring of levels is advised, if used. Lactation Compatible with breastfeeding.
	BD dosing 7.5mg/kg every 12 hours (Maximum 750mg BD)	NTM e.g. <i>Mycobacterium abscessus</i> (BD dosing only)	BD dosing <500mg, slow IV bolus ≥ 500mg, in 100mL sodium chloride 0.9% over 30 minutes	BD dosing Trough must be <5mg/L; Aim 1 hour post dose peak 20-30mg/L Hepatic effects No precautions necessary Renal Impairment GFR 20-50mL/min 6mg/kg BD, adjusted according to peak and trough levels GFR<20mL/min 6mg/kg every 12-24 hours (adjust frequency according to levels)	

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Aztreonam	2g every 8 hours (<35kg max. 50mg/kg TDS)	Narrow spectrum of activity against gram-negatives including <i>H.influenzae</i> and <i>P.aeruginosa</i> . No anti gram-positive activity, therefore usually used in combination with an aminoglycoside or colistin	Slow IV bolus over 3-5 minutes	Hepatic effects No specific precautions: Monitor closely Renal impairment GFR 30-50mL/min Dose as in normal renal function GFR 10-30mL/min 2g loading dose then reduce to 1g TDS GFR <10mL/min 2g loading dose then reduce to 500mg TDS	Pregnancy No reports of use in human pregnancy. Animal data suggest low risk. But absence of human pregnancy experience prevents a more complete assessment of the embryo-foetal risk. Use only if not possible to use antibiotics known to be safe in pregnancy. Lactation Compatible with breastfeeding
Cefoxitin	Usually 2-3g QDS (max 12g/day) (200mg/kg/day in 3-4 divided doses)	<i>Mycobacterium abscessus</i> NOT active against <i>Pseudomonas aeruginosa</i>	IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	Hepatic effects Transient elevations in AST, ALT, ALP and serum LDH have been reported; Jaundice has also been noted. Renal impairment GFR 30-50mL/min Max 2g TDS GFR 10-30mL/min 2g loading dose then 2g BD GFR 5-10mL/min 2g loading dose then 1g BD GFR <5mL/min 2g loading dose then 1g OD	Pregnancy No detectable teratogenic risk in a large 2001 study. Safe in all trimesters. Lactation Compatible with breastfeeding

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Ceftazidime	Intermittent dosing	<i>Pseudomonas aeruginosa</i> ; <i>B. cepacia</i> ; <i>S. maltophilia</i>	Intermittent dosing	Hepatic effects No need to adjust doses in mild to moderate hepatic impairment. Transient elevations in one or more liver enzymes common; jaundice has been reported. Monitor closely in severe impairment. Renal impairment GFR 31-50mL/min 2g BD GFR 16-30mL/min 2g OD GFR 6-15mL/min 1g OD GFR <5mL/min 1g every 48h	Pregnancy No detectable teratogenic risk in a large 2001 study. Safe in all trimesters. Lactation Compatible with breastfeeding.
	2-3g every 8 hours.		IV bolus over 3-5 minutes		
	(<35kg Max. 50mg/kg TDS)		Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes		
	Continuous infusion		Continuous infusion		
	12g over 24h		Reconstitute each 2g vial with 20mL WFI. Infuse 4g (40mL) over 8h then repeat.		

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Chloramphenicol	<p>12.5-25mg/kg QDS (usually 500mg).</p> <p>Max. 1g QDS</p> <p>Avoid repeat courses within 3 months of last course.</p>	<p>Anecdotal reports of a clinical response in patients with <i>P.aeruginosa</i> and <i>B.cepacia</i> complex</p>	<p>Bolus over at least 1 minute.</p> <p>Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.</p>	<p>Hepatic effects</p> <p>Avoid if possible in hepatic impairment. If not possible, reduced dose may be required to maintain trough level <10mg/L.</p> <p>Renal Impairment</p> <p>GFR 20-50mL/min Dose as in normal renal function</p> <p>GFR 10-20mL/min Dose as in normal renal function</p> <p>GFR <10mL/min Dose as in normal renal function</p> <p>Manufacturers recommend monitoring levels in patients with renal impairment. Therapeutic range: peak = 10-20 mg/L (0.5-1.5h after IV dose); trough = 5-10 mg/L.</p>	<p>Pregnancy</p> <p>Not associated with increased incidence of congenital malformations. Concerns that use near term may be associated with a risk of neonatal Gray Baby Syndrome are not supported by evidence. However, UK recommendations are that during pregnancy, the use of systemic chloramphenicol should be reserved for life-threatening illness.</p> <p>Lactation</p> <p>An alternate drug is preferred to chloramphenicol during breastfeeding, especially while nursing a newborn or preterm infant. If the mother must receive chloramphenicol during nursing, monitor the infant for gastrointestinal disturbances and adequacy of nursing. Monitoring of the infant's complete blood count and differential is advisable. In some cases, discontinuation of breastfeeding might be preferred.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Ciprofloxacin	400mg every 12 hours	<i>P. aeruginosa</i>	Infuse over 60 minutes	<p>Hepatic effects No dose adjustments necessary in hepatic impairment. Increased transaminases and bilirubin are uncommon.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min 400mg BD GFR <10mL/min 200mg BD</p>	<p>Pregnancy Limited evidence does not suggest any increased risk of adverse pregnancy outcomes – treatment should not be withheld if indicated.</p> <p>Lactation Fluoroquinolones have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, recent studies indicate little risk. The calcium in milk might prevent absorption of the small amounts of fluoroquinolones in milk, but insufficient data exist to prove or disprove this.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Colistimethate	<p><40kg – 1MU every 8 hours</p> <p>> 40kg – 2MU every 8 hours</p>	<p><i>P. aeruginosa</i></p> <p>NOT active against <i>B. Cepacia</i> complex</p>	<p>Bolus administration is routine practice at RBH on respiratory wards.</p> <p>Via totally implanted venous access device (TIVAD, Port): Reconstitute with 10-20mL water for injections and administer over 5 minutes.</p> <p>Via venflon/long line: Reconstitute with 20-40mL water for injections and administer over 5 minutes.</p> <p>Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.</p>	<p>Hepatic effects No specific precautions</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min 1MU BD (max. 50% of usual dose for weight) GFR <10mL/min 1MU every 18-24 hours (max. 30% usual dose for weight)</p>	<p>Pregnancy There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus^{SPC}.</p> <p>Lactation Colistimethate is excreted into breastmilk at a low level which may cause modification of infant bowel flora^{BRIGGS}.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Co-trimoxazole	960mg – 1.44g every 12 hours (<35kg Max. 27mg/kg)	Used mainly for <i>S. maltophilia</i> . Useful active against <i>S. aureus</i> , <i>H. influenzae</i> and may be useful for <i>B. cepacia</i> .	960mg – 250ml 0.9% sodium chloride over 60 minutes 1.44g – 500ml 0.9% sodium chloride over 90 minutes	<p>Hepatic effects Increased LFTs and bilirubin, hepatic necrosis and cholestatic jaundice have been rarely reported. No data are available relating to dosage in patients with impaired hepatic function. Contra-indicated in patients showing marked liver parenchymal damage.</p> <p>Renal Impairment GFR 30-50mL/min Dose as in normal renal function GFR <30mL/min 50% of normal dose, i.e. 480 – 720mg BD</p>	<p>Pregnancy Potential increased risk of hyperbilirubinaemia with sulphonamide-containing medicines during pregnancy in neonates with other risk factors.</p> <p>No overall increased risk of congenital malformation has been demonstrated with trimethoprim use in human pregnancy, although an increased risk of neural tube defects, cleft lip/palate and cardiac defects has been reported.</p> <p>Folate supplementation may reduce risks: high dose (5mg) folic acid is recommended in all women treated with trimethoprim (and therefore co-trimoxazole) during the first trimester as a precautionary measure.</p> <p>Lactation No reports found regarding neonatal toxicity following exposure to trimethoprim during lactation. With healthy, full-term infants it appears acceptable to use sulfamethoxazole and trimethoprim during breastfeeding after the newborn period.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Flucloxacillin	1-2g every 6 hours (50mg/kg QDS)	<i>S. aureus</i>	IV bolus over 3-5 minutes	<p>Hepatic effects Changes in LFT results may occur: reversible when treatment is discontinued. Hepatitis and cholestatic jaundice have been reported, and are not related to dose or route of administration; administration for more than two weeks and increasing age are risk factors. The onset of these effects may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months.</p> <p>Contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction. Use with caution in patients with hepatic dysfunction.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min Dose as in normal renal function up to a total daily dose of 4g</p> <p>Monitor urine for protein at high doses</p>	<p>Pregnancy Considerable clinical experience has not indicated adverse fetal effects when flucloxacillin is used in pregnancy.</p> <p>Lactation Penicillins and cephalosporins are the antibiotics of choice during breastfeeding. However, trace quantities of flucloxacillin can be detected in breast milk: the possibility of hypersensitivity reactions must be considered in breast-feeding infants.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Fosfomycin	4g every 6 hours	<i>Pseudomonas aeruginosa</i>	<p>250ml 5% dextrose over 60 minutes</p> <p>Can also be infused in 200mL WFI: Reconstitute the 4g vial, withdraw two 2g aliquots and add to each of two 100mL WFI – infuse sequentially over 30 minutes (total 60 minutes)</p>	<p>Hepatic effects Temporary increases in transaminases and alkaline phosphatase have been observed.</p> <p>Renal Impairment GFR 20-40mL/min 4g every 12 hours GFR 10-20mL/min 4g every 24 hours GFR <10mL/min 4g every 48 hours</p>	<p>Pregnancy Lack of teratogenicity in animals and apparently safe use during human pregnancy appear to indicate that it presents a low risk to foetus – compatible with pregnancy.</p> <p>Lactation A small quantity passes into breast milk – although limited human data, probably compatible.</p>
Meropenem	<p>2g every 8 hours</p> <p>(Reduce to 1g TDS if adverse effects)</p>	<i>Pseudomonas aeruginosa</i> ; <i>B.cepacia</i> complex; <i>Mycobacterium abscessus</i>	<p>Each 1g vial must be reconstituted with 20ml water and given as an IV bolus over 3-5 minutes</p> <p>Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.</p>	<p>Hepatic effects Increased transaminases, ALP and lactate dehydrogenase are common; increased bilirubin uncommon: monitor in those with pre-existing liver disorders. No dose adjustment is necessary in hepatic impairment; however, local practice is to try 1g TDS in those with persistently elevated transaminases on higher dose.</p> <p>Renal Impairment GFR 20-50mL/min 2g BD GFR 10-20mL/min 1g BD GFR <10mL/min 1g OD</p>	<p>Pregnancy There is limited human data, animal studies suggest low risk. Animal studies have shown no evidence of impaired fertility or foetal harm. The near absence of published human pregnancy data doesn't allow an assessment of embryo-foetal risk. Imipenem-cilastin is considered safe to use after 28 weeks gestation and meropenem is most likely can be classed similarly. The foetal risk pre-28 weeks is unknown.</p> <p>Lactation No reports of use of meroepem during lactation. Potential effect on infant unknown but probably compatible.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Piperacillin/tazobactam	4.5g every 6 – 8 hours (Max 4.5g QDS) (90mg/kg)	<i>Pseudomonas aeruginosa</i>	IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	<p>Hepatic effects Monitor hepatic function. No dosage adjustment necessary in hepatic impairment. Increases in transaminases are uncommon; increased bilirubin, ALP, GGT and hepatitis are rare.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Max 4.5g TDS GFR <10mL/min 4.5g BD</p>	<p>Pregnancy Human data are very limited. No foetal harm was observed in animals. There is substantial experience with penicillins in human pregnancy that have shown this class of drugs are safe. Tazobactam is probably safe in pregnancy.</p> <p>Lactation Although no information is available on the use of piperacillin and tazobactam during breastfeeding, limited information indicates that maternal doses of piperacillin produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Piperacillin and tazobactam is acceptable to use during breastfeeding.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Teicoplanin	400mg every 12 hours for 3 doses then 400mg once daily	Methicillin resistant <i>S. aureus</i> (MRSA)	<p>Reconstitute with diluent supplied. Usually given by IV bolus over 3-5 minutes.</p> <p>Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.</p>	<p>Hepatic effectsⁱ May cause transient abnormalities in transaminases and ALP. Liver function should be monitored, but no dosage adjustments necessary in impairment.</p> <p>Renal Impairmentⁱⁱ GFR 20-50mL/min Give normal loading dose then dose as in normal renal function GFR 10-20mL/min Give normal loading dose then dose as in normal renal function GFR <10mL/min Give normal loading dose then 400mg every 48h</p>	<p>Pregnancy</p> <p>No adequate data from the use of teicoplanin in human pregnancy. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Teicoplanin should not be used during pregnancy unless clearly necessary^{spc}.</p> <p>Lactation</p> <p>It is not known whether teicoplanin is excreted in human breast milk. The excretion of teicoplanin in milk has not been studied in animals^{spc}.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Temocillin	2g every 12 hours	<i>B. cepacia</i> complex NO activity against <i>Pseudomonas aeruginosa</i>	IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	Hepatic effects Limited experience in patients with impaired hepatic function has not indicated a need for a reduction in dosage. Renal Impairment GFR 30-50mL/min Dose as in normal renal function GFR 10-30mL/min 2g OD GFR <10mL/min 2g every 48h	Pregnancy Animal studies with temocillin have shown no teratogenic effects. There is no experience of temocillin in human pregnancy. However, temocillin is a penicillin; this class of drugs are known to be safe in all trimesters. Lactation There is no information on the use of temocillin in lactation. However it is known that penicillins are compatible with breastfeeding.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Tigecycline	<p>50mg every 12 hours (we do not routinely give loading dose due to nausea)</p> <p>Reduce to 25mg every 12 hours if 50mg not tolerated</p>	<p><i>Mycobacterium abscessus</i></p> <p>Resistant <i>achromobacter xyloxidans</i></p> <p><i>Stenotrophoma s maltophilia</i></p>	<p>Add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.</p> <p>Ensure regular IV ondansetron (or alternative if required) also prescribed – highly emetogenic – risk of treatment failure if cannot tolerate.</p>	<p>Hepatic effects Elevated transaminases and bilirubin common. Jaundice and liver injury (mostly cholestatic) uncommon. No dose reduction required in mild to moderate liver impairment (Child-Pugh Class A and B). In severe liver disease (Child-Pugh Class C), 100mg loading dose then 25mg BD. Use with caution and monitor clinical response.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min Dose as in normal renal function</p>	<p>Pregnancy No reports of the use of tigecycline in human pregnancy. In one animal species exposures close to those in humans that did not cause maternal toxicity did result in reduced foetal weight and minor skeletal abnormalities. Tigecycline crosses the placenta of rats and rabbits and enters foetal tissue including bony structures. Tigecycline can permanently discolour teeth if used in the second half of pregnancy. Use in 1st trimester does not represent a major risk to foetus but use in 2nd and 3rd trimesters should be avoided.</p> <p>Lactation There are no reports of the use of tigecycline use during human lactation. It is likely to be excreted into breast milk but there may be little or no systemic exposure.</p>

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Timentin (ticarcillin/ clavulanic acid)	3.2g every 6 hours (80mg/kg)	<i>Pseudomonas aeruginosa</i> May be useful for <i>Stenotrophomonas maltophilia</i>	Add reconstituted drug to 100mL water for injections and administer over 30 minutes. (If hyponatraemia is a problem, can be added to 100mL 5% dextrose to administer)	Hepatic effects Monitor liver function: can cause cholestatic jaundice, increase in LFTs and transient hepatitis. Cholestatic jaundice may occur during use or soon after treatment cessation. Use with caution in patients with evidence of severe hepatic dysfunction. Renal Impairment GFR 30-50mL/min 3.2g TDS GFR 10-30mL/min 1.6g TDS GFR <10mL/min 1.6g BD	Pregnancy No reports linking the use of ticarcillin have been reported. Although experience is limited, all penicillins are considered low risk in pregnancy. Several studies have described the safe use of clavulanic acid in pregnant women. Lactation Compatible with breastfeeding.
Tobramycin	7mg/kg once daily Max dose 660mg once daily.	<i>Pseudomonas aeruginosa</i> <i>Burkholderia cepacia</i> complex	100ml 0.9% sodium chloride over 30 minutes	GFR 20-50 – 3mg/kg od Avoid if GFR < 20ml/min	Pregnancy No reports linking the use of tobramycin with congenital defects. Not teratogenic in 2 animal species. Ototoxicity has not been reported as an effect of in utero exposure. However, eighth cranial nerve toxicity in the foetus is well known following exposure to other aminoglycosides and may potentially occur with tobramycin. Lactation Compatible with breastfeeding.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Vancomycin	1g every 12 hours	MRSA	250ml 0.9% sodium chloride over 100 minutes	<p>Hepatic effects No dose adjustments necessary.</p> <p>Renal Impairment (starting dose; adjust according to levels) GFR 20-50mL/min 500mg-1g od-bd GFR 10-20mL/min 500mg-1g every 24 to 48 hours GFR <10mL/min 500mg-1g every 48 to 96 hours</p> <p>Therapeutic Drug Monitoring Trough levels should be 10-15mg/L. Check trough level just before 4th dose. Level <10mg/L: increase maintenance dose by 500mg daily and repeat level after 48h. Level 15-20mg/L: continue if patient tolerating. Level 20-25mg/L: if next dose not yet given, reduce by 500mg daily without omitting any doses; if the dose has already been given, omit one dose and then reduce maintenance dose by 500mg daily.</p>	<p>Pregnancy There are no known cases of congenital defects. The manufacturer has received reports of use in pregnancy without any adverse foetal effects.</p> <p>Lactation Limited information indicates that vancomycin produces low levels in milk and it would not be expected to be absorbed or cause any adverse effects in breastfed infants.</p>

13.33: Oral Antifungals

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Fluconazole	Candidiasis associated with antibiotic use: 100mg daily for duration of antibiotic course	Patients should be warned about the potential for dizziness and should be advised not to drive or operate machines if any of these symptoms occur.	<p>Hepatic effects Monitor liver function. Hepatotoxicity including raised LFTs is usually reversible on discontinuation. Hepatic necrosis rarely observed. Toxicity increased with concomitant use of hepatotoxic drugs. Discontinue if clinical signs/symptoms occur.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min 50% of normal dose</p>	<p>Pregnancy Use of fluconazole during 1st trimester appears to be teratogenic with continuous daily doses of 400mg/day or more; malformations may resemble those observed in Antley-Bixler Syndrome. Due to limited available safety data, high dose fluconazole use during pregnancy should be avoided unless compellingly indicated.</p> <p>Lactation Compatible with breastfeeding – if possible, the dose should be taken at night after the last breast-feed.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Itraconazole	<p>Usual starting dose: 200 mg BD</p> <p>May be increased according to levels</p>	<p>Capsules are poorly absorbed in CF. Use liquid where possible (limited due to taste).</p> <p>Liquid should ideally be taken one hour before food.ⁱⁱⁱ Capsules should be taken immediately after a meal for maximal absorption or with acidic drink e.g. cola/orange in patients taking acid secretion suppressors.</p>	<p>Hepatic effects</p> <p>Prolonged half-life in cirrhotic patients whilst oral bioavailability is decreased – adjust dose according to levels. Elevations in liver enzymes, hepatitis, serious hepatotoxicity, fatal acute liver failure is very rare. Monitor LFTs during treatment and should be stopped if signs or symptoms suggestive of hepatitis are present. If pre-existing liver disease or has experienced liver toxicity with other drugs then treatment must only be started if benefit exceeds risk of liver injury.</p> <p>Renal impairment (all levels) Dose as in normal renal function</p> <p>Therapeutic Drug Monitoring Target trough 0.5 – 2.0mg/L (parent molecule) or 1.0 – 4.0mg/L (parent molecule + metabolite. (Parent + metabolite indicates potential total biological activity).</p>	<p>Pregnancy</p> <p>Human pregnancy data suggests that the risk of foetal toxicity is low. The animal data cannot be adequately interpreted because maternal toxicity was evident and comparisons with human data were based on body weight. Safest to avoid, especially in 1st trimester.</p> <p>Lactation</p> <p>Excreted into breast milk - effects of long term exposure on the infant has not been studied, therefore not recommended.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Voriconazole	<p><40 kg: 200 mg BD for 1 day then 100 mg BD</p> <p>>40 kg: 400 mg BD for 1 day then 200 mg BD</p> <p>Doses may be increase according to levels. Non linear pharmacokinetics: increase doses cautiously – refer to pharmacist for advice on doses >200mg BD.</p> <p>(We have occasionally increased cautiously to 400mg BD)</p>	<p>Photosensitivity – avoid exposure to sunlight. Use high factor sun block up to 4 weeks post treatment. Refer to dermatologist if photosensitivity reaction occurs. Risk of squamous cell carcinoma of the skin has been reported on long term use in patients with photosensitivity and other risk factors.</p> <p>Monitor visual function and renal function with long term use.</p>	<p>Hepatic effects</p> <p>Associated with elevations in LFT's and clinical signs of liver damage such as jaundice. No dose adjustment is necessary in patients with acute hepatic injury manifested by elevated LFT's (monitor for further increases). Patients with hepatic impairment must be carefully monitored for drug toxicity.</p> <p>Mild to moderate hepatic impairment (Child-Pugh A and B): Standard loading dose; 50% usual maintenance dose.</p> <p>Severe hepatic impairment (Child-Pugh C): No information available.</p> <p>Renal Impairment</p> <p>GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min Dose as in normal renal function</p> <p>Therapeutic Drug Monitoring</p> <p>Serum levels should be measured after 3 days of commencing therapy or dose changes, take sample just before the next oral dose. Dose escalation is advised for any level less than 1.3mg/L.</p>	<p>Pregnancy</p> <p>No reports in human pregnancy available; animal data suggests risk of toxicity and teratogenicity. Avoid.</p> <p>Lactation</p> <p>Voriconazole is expected to be excreted into breast-milk therefore potential for toxicity in nursing infants, especially during the neonatal period. Women taking voriconazole should avoid breastfeeding.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Posaconazole	<p>400 mg BD</p> <p>May need to adjust according to levels – we have occasionally increased to 400mg TDS.</p>	<p>Take dose immediately following a meal to enhance absorption. If not possible, may need to use 200mg QDS dosing.</p>	<p>Hepatic effects</p> <p>Monitor liver function before and during treatment. Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) demonstrate an increase in plasma exposure, but do not suggest that dose adjustment is necessary – monitor levels.^{iv} Increases in liver enzymes & bilirubin may be observed and are reversible on discontinuation. Hepatitis, jaundice, hepatomegaly, hepatic failure, cholestasis also observed.</p> <p>Renal Impairment</p> <p>(all levels) Dose as in normal renal function^v</p> <p>Therapeutic Drug Monitoring</p> <p>Serum levels should be monitored where indicated e.g. interacting drug commenced or efficacy not observed – random sample after 1-2 weeks on oral therapy should be >0.7mg/L.</p>	<p>Pregnancy</p> <p>There are no reports on use in pregnancy. Animal data suggest risk of toxicity. Avoid during pregnancy, especially in 1st trimester.</p> <p>Lactation</p> <p>No reports in human lactation. Avoid as potentially toxic to infant.</p>

13.4: Intravenous Antifungals

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Amphotericin B Liposomal (Ambisome®)	<i>Aspergillus</i> spp. <i>Candida</i> spp.	Test dose: 1mg (Day 1 only)	Infuse from prepared amphotericin (see below) over 10 minutes; stop the infusion and observe patient for 30 minutes. If no reaction proceed with remainder of the infusion.	Hepatic effects No data to indicate need to alter dose in hepatic dysfunction. Monitor hepatic function: abnormal LFT's, hyperbilirubinaemia and increased ALP common. Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min Dose as in normal renal function Use with caution with other nephrotoxic antibiotics e.g. aminoglycosides, colomycin.	Pregnancy No adverse effects have been reported in exposed human embryos and foetuses. Lactation No reports regarding use during human lactation have been located. ^{vi} However, as oral absorption is minimal, and due to high protein binding and molecular weight as well as its use in paediatrics, it is unlikely the amount in milk would be clinically relevant to a breastfeeding infant.
		If tolerated: Day 1: 1mg/kg OD Thereafter 3mg/kg OD – can be increased to 5mg/kg OD if necessary.	Dilute to final concentration 0.2 – 2mg/L with 5% glucose and infuse over 30-60 minutes. CIVAS available during pharmacy opening hours.		

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Caspofungin	<i>Aspergillus</i> spp. <i>Candida</i> spp. <i>Exophiala</i> spp.	Single 70mg loading dose, then: <80kg: 50mg OD >80kg: 70mg OD	Add reconstituted drug to 250mL sodium chloride 0.9% and administer over 60 minutes.	<p>Hepatic effects</p> <p>Monitor liver function: elevations in ALT, AST, ALP and bilirubin are common. Cholestasis, hepatotoxicity and abnormal hepatic function uncommon.</p> <p>Mild hepatic impairment (Child-Pugh A): No dose adjustment necessary.</p> <p>Moderate hepatic impairment (Child-Pugh B): 70mg loading dose then 35mg on</p> <p>Severe impairment (Child-Pugh C): No clinical experience.</p> <p>Renal Impairment</p> <p>GFR 20-50mL/min Dose as in normal renal function</p> <p>GFR 10-20mL/min Dose as in normal renal function</p> <p>GFR <10mL/min Dose as in normal renal function</p>	<p>Pregnancy</p> <p>No reports in human pregnancy available; animal data suggest risk, especially if exposure occurs in the 1st trimester. If indicated, maternal treatment should avoid the 1st trimester if possible.</p> <p>Lactation</p> <p>No data available for human milk. Oral bioavailability reported to be poor therefore unlikely an infant would absorb enough to be clinically relevant.^{vii} As the risk of harm from exposure to caspofungin appears to be low, women being treated with caspofungin should be allowed to breast feed. Infants should be monitored for signs and symptoms of histamine release and GI complaints.</p>

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Fluconazole	<i>Candida spp.</i>	400mg OD (<35kg maximum 12mg/kg/d)	Administer at a rate not exceeding 5-10mL/minute (10-20mg/minute).	<p>Hepatic effects Monitor liver function. Hepatotoxicity including raised LFTs is usually reversible on discontinuation. Hepatic necrosis rarely observed. Toxicity increased with concomitant use of hepatotoxic drugs. Discontinue if clinical signs/symptoms occur.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min 50% of normal dose</p>	<p>Pregnancy Use of fluconazole during 1st trimester appears to be teratogenic with continuous daily doses of 400mg/day or more; malformations may resemble those observed in Antley-Bixler Syndrome. Due to limited available safety data, high dose fluconazole use during pregnancy should be avoided unless compellingly indicated.</p> <p>Lactation Compatible with breastfeeding – if possible, the dose should be taken at night after the last breast-feed.</p>

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Voriconazole	<i>Aspergillus</i> spp. <i>Candida</i> spp <i>Exophiala</i> spp. <i>Scedosporium</i> spp.	Loading dose: 6mg/kg 12 hourly for 2 doses then; Maintenance dose: 4mg/kg BD	Further dilute reconstituted voriconazole to 0.5 – 5mg/mL in 0.9% sodium chloride. Administer at a rate of not more than 3mg/kg/hour over 1-3h.	<p>Hepatic effects</p> <p>Associated with elevations in LFT's and clinical signs of liver damage such as jaundice. No dose adjustment is necessary in patients with acute hepatic injury manifested by elevated LFT's. Patients with hepatic impairment must be carefully monitored for drug toxicity.</p> <p>Mild to moderate hepatic impairment (Child-Pugh A and B): Standard loading dose; 50% usual maintenance dose.</p> <p>Severe hepatic impairment (Child-Pugh C): No information available.</p> <p>Renal Impairment</p> <p>GFR 20-50mL/min Dose as in normal renal function</p> <p>GFR 10-20mL/min Dose as in normal renal function</p> <p>GFR <10mL/min Dose as in normal renal function</p>	<p>Pregnancy</p> <p>No reports in human pregnancy available; animal data suggests risk of toxicity and teratogenicity. Avoid.</p> <p>Lactation</p> <p>Voriconazole is expected to be excreted into breast-milk therefore potential for toxicity in nursing infants, especially during the neonatal period. Women taking voriconazole should avoid breastfeeding.</p>

13.5: Inhaled Antimicrobials

13.5.1: Nebulised Antimicrobials

Drug	Indication	Dose	Nebuliser devices	Reconstitution/dilution	Counselling and storage	Pregnancy and lactation
Amikacin	<i>Mycobacterium abscessus</i>	500 mg BD Use 500mg/2mL IV preparation (we use Hospira UK brand)	Vibrating mesh nebuliser	Use neat	Possible adverse effects: aminoglycoside-related ototoxicity, bronchoconstriction, mouth soreness. Once opened, ampoules and vials should be used immediately	There have been no reports linking the use of amikacin to congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. Eighth cranial nerve toxicity in the fetus has, however, been reported after exposure to other aminoglycosides (kanamycin and streptomycin). Amikacin could potentially cause this, however, as absorption following inhalation of aminoglycosides is likely to be minimal and the maternal systemic concentration low, amikacin may be considered if maternal benefits outweigh risk to foetus.
			Jet nebuliser and compressor	Further dilute to 4mL with sodium chloride 0.9%	Stop if tinnitus or hearing loss develops. Stop temporarily if on IV aminoglycosides.	

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Amphotericin (Fungizone® 50mg IV preparation)	<i>Aspergillus fumigatus</i>	Initially 5mg twice daily. Increase in steps of 5mg up to 0.5mg/kg (max 25mg) twice daily. There is usually no need to use the liposomal formulation (Ambisome®) for nebulisation, however, this may be considered if essential in those who do not intolerant Fungizone®	Jet nebuliser	Reconstitute a 50mg vial with 10mL water for injections to produce a 5mg/mL solution. Withdraw the required amount and further dilute if necessary to minimum 3mL with water for injections. DO NOT mix with sodium chloride 0.9%	Once reconstituted, the remainder of the vial may be stored in a refrigerator for up to 24h at 2-8°C for the next 1-2 doses.	No reports linking the use of amphotericin with congenital defects located. Compatible with pregnancy.

Drug	Indication	Dose	Nebuliser devices	Reconstitution/dilution	Counselling and storage	Pregnancy and lactation
Aztreonam Lysine (Cayston®)	<i>Pseudomonas aeruginosa</i>	75 mg TDS on alternate months	Altera Nebuliser Handset and Altera Aerosol Head (supplied with the drug) connected to an Altera Control Unit or an eFlow rapid Control Unit	Reconstitute the lyophilised aztreonam lysine with 1mL solvent supplied (0.17% w/v sodium chloride)	Once reconstituted, use immediately. Powder vial and solvent ampoule must be stored in a refrigerator (2-8°C). May be stored outside a refrigerator at up to 25°C for up to 28 days.	There are no data from the use of aztreonam in pregnant women, however, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Systemic concentration of aztreonam following inhaled administration of nebulised aztreonam is low. Furthermore, beta lactam antibiotics can be used during pregnancy when strongly indicated. Nebulised aztreonam may therefore be used during pregnancy where the clinical condition of the woman requires treatment.
Ceftazidime	<i>Burkholderia cepacia</i>	1g bd	Jet nebuliser only Mesh nebuliser systems (i-Neb ADD and eFlow) should not be used	Reconstitute a 1g vial with 3mL water for injections		If clinically indicated, cephalosporins may be used at any stage during pregnancy.

Drug	Indication	Dose	Nebuliser devices	Reconstitution/dilution	Counselling and storage	Pregnancy and lactation
Colistimethate sodium (colistin) (Colomycin®, Promixin®)	Eradication/suppression of <i>Pseudomonas aeruginosa</i> lung infection	iNeb: 1 million units BD (Promixin)	With i-Neb ADD System only (Grey chamber)	Reconstitute 1MU Promixin vial with 1mL sodium chloride 0.9%	Colomycin® can be reconstituted with salbutamol (2.5 to 5mg) if the patient experiences bronchoconstriction	There is no data on nebulised colistin but experience suggests this is safe in pregnancy.
		Other nebulisers: 2 million units BD (we have used TDS in certain circumstances)	eFlow Jet nebuliser	Reconstitute the contents of the 2 million unit vial with 2-4mL (depending on nebuliser device) sodium chloride 0.9% or water for injections		
Meropenem (500mg powder for reconstitution IV preparation)	<i>Mycobacterium abscessus</i> ; <i>Burkholderia cepacia</i>	250mg BD	E-Flow Jet nebuliser and compressor The i-Neb ADD system should not be used	Reconstitute a 500mg vial with 10mL sodium chloride 0.9% and withdraw 5mL (250mg).	If reconstituted to give a final concentration of 50mg/mL with sodium chloride 0.9%, the remainder of the vial can be stored in a fridge at 2-8°C for up to 18 hours for the next dose.	No information available in human pregnancy therefore use cannot routinely be recommended. Animal studies have shown no evidence of impaired fertility or foetal harm. Meropenem by nebulisation should be considered if the maternal benefit outweighs the risk to the foetus.
				Alternatively, can be reconstituted with Water for Injections (2 nd line) and withdraw 5mL (250mg) (note reduced expiry time).	If reconstituted to give a final concentration of 50mg/mL with water for injections, the remainder of the vial can be stored in a fridge at 2-8°C for up to 12 hours for the next dose.	

Drug	Indication	Dose	Nebuliser devices	Reconstitution/dilution	Counselling and storage	Pregnancy and lactation
Taurolidine	<i>Burkholderia cepacia</i> (unresponsive to standard antibiotic options)	Usually 2-5ml of the 2% solution BD	Jet nebuliser and compressor	Use neat	Once in use, each bottle may be stored in a refrigerator and used for up to 7 days.	No information available in human pregnancy therefore use cannot routinely be recommended.
Temocillin	<i>Burkholderia cepacia</i>	1g BD	Jet nebuliser and compressor	Reconstitute a 1g vial with 3mL water for injections		No information available in human pregnancy therefore use cannot routinely be recommended. However, penicillins are known to be safe in pregnancy and lactation.

Drug	Indication	Dose	Nebuliser devices	Reconstitution/dilution	Counselling and storage	Pregnancy and lactation
<p>Tobramycin preservative-free solution for nebulisation</p> <p>BRAMITOB® or TOBI®</p>	<p>Long-term management of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i></p>	<p>300mg BD on alternate months</p>	<p>i-Neb (Lilac chamber)</p> <p>eFlow</p> <p>Jet nebuliser and compressor</p>	<p>Ready to use solution.</p> <p>Do not mix with any other solution for nebulisation.</p>	<p>BD dosing should ideally be 12 hourly. If a shorter interval between morning & evening doses is needed, the interval should not be less than 6 hours.</p> <p>Store at 2 – 8 °C, in the original container.</p> <p>After removal from refrigerator, TOBI® pouches (intact or opened) may be stored at up to 25°C for up to 28 days; Bramitob® pouches (intact or opened) may be stored at up to 25°C for up to 3 months</p> <p>Stop if tinnitus or hearing loss develops. Stop temporarily if on IV aminoglycosides.</p>	<p>There have been no reports linking the use of tobramycin to congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. Eighth cranial nerve toxicity in the fetus has, however, been reported after exposure to other aminoglycosides. Tobramycin could potentially cause this, however, as absorption following inhalation of aminoglycosides is likely to be minimal and the maternal systemic concentration low, tobramycin may be considered if maternal benefits outweigh risk to foetus.</p>

Section 5.2 Dry Powder Inhalers

Drug	Indication	Dose	Counselling and storage	Pregnancy and lactation
Colobreathe®	Long-term management of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i>	1,662,500 units BD	N/A	There is no data on nebulised colistin but experience suggests this is safe in pregnancy.
Tobi Podhaler®	Long-term management of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i>	112mg BD	N/A	There have been no reports linking the use of tobramycin to congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. Eighth cranial nerve toxicity in the fetus has, however, been reported after exposure to other aminoglycosides. Tobramycin could potentially cause this, however, as Systemic exposure following inhalation of TOBI Podhaler is very low, it may be considered if maternal benefits outweigh risk to foetus. The manufacturer recommends that patients who use TOBI Podhaler during pregnancy, or become pregnant while taking TOBI Podhaler, should be informed of the potential hazard to the foetus.

Section 6: Mucolytics

Drug	Route	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy
Hypertonic saline solution Nebusal® 7% 4mL amps	Nebulised pre-physio	Adults: 4mL of 3.5% or 7% BD	Pre-treat with bronchodilator For 3.5% solution: dilute 7% solution with an equal volume of water for injections	Hepatic effects Minimal systemic absorption so very unlikely to affect liver function Renal Impairment Minimal systemic absorption so very unlikely to affect renal function	Pregnancy Safe in all trimesters. Lactation Safe in breastfeeding
N-acetylcysteine 20% (200 mg/mL) injection	Nebulised 30 min pre-physio	3 – 4mL of 50 – 100 mg/mL 2 – 4 times a day	NOT granules. Forewarn patients – tastes and smells unpleasant. 50 mg/mL: dilute 1mL 20% with 3mL WFI 100 mg/mL: dilute 1.5mL 20% with 1.5mL WFI If only a proportion of the ampoule is used the remainder may be transferred to a plastic syringe, <u>stored in a refrigerator at 2-8°C up to 96 hours</u> for subsequent doses.	Hepatic effects Minimal systemic absorption so very unlikely to affect liver function Renal Impairment Minimal systemic absorption so very unlikely to affect renal function	Pregnancy No experience as mucolytic in human pregnancy but likely compatible Lactation Compatible with breastfeeding
Dornase alfa (rhDNase) Pulmozyme®	Nebulised 1 hour pre-physio	2.5mg OD. May be increased to BD if required	3 month trial to assess effect	Hepatic effects Minimal systemic absorption so very unlikely to affect liver function Renal Impairment Minimal systemic absorption so very unlikely to affect renal function	Pregnancy No human data. Animal data suggests no placental transfer. Our experience of use in pregnancy suggests safe in pregnancy. Lactation Compatible with breastfeeding

Drug	Route	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy
Mannitol Bronchitol®	Inhaled 30 min pre-physiotherapy.	400mg (10 x 40mg capsules) BD	Use after dornase alfa, if applicable.	<p>Hepatic effects</p> <p>Mannitol has not specifically been studied in patients with impaired hepatic function. Data from studies suggest that no dose adjustments are required.</p> <p>Renal Impairment</p> <p>Mannitol has not specifically been studied in patients with impaired renal function. Data from studies suggest that no dose adjustments are required.</p>	<p>Pregnancy</p> <p>There are limited data from the use of mannitol in pregnant women. Animal studies do not indicate direct or indirect harmful effects..As the effects of a possible hyperresponsive reaction on the mother and/or foetus are unknown, caution should be exercised when prescribing mannitol to pregnant women.</p> <p>Lactation</p> <p>Unknown if excreted into breastmilk.</p>

Section 7: Gastrointestinal

Section 7.1: Pancreatic Enzyme Replacement Therapy (PERT)

Drug	Dose		Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Creon Micro (Protease 200 units, lipase 5000 units, amylase 3600 units per 100mg)	Pancreatic insufficiency	Initially 100mg (1 measure) with each meal	Dose should be gradually increased according to response and tolerance Capsules should be swallowed whole or may be opened and both granules and capsules must be taken with acidic fluid e.g. orange, apple or pineapple juice or soft food e.g apple puree or yogurt, but without chewing and taken immediately.	Hepatic Effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy No clinical data on exposed pregnancies available, although animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. Lactation Can be used during breast – feeding.
Creon 10,000, 25, 000 and 40,000		1-2 capsules initially with each meal			
Pancrex V powder (protease 1400 units, lipase 25,000 units, amylase 30,000 units/g)	Pancreatic insufficiency	0.5-2g before each meal & snack	Dose should be gradually increased according to response and tolerance Can be swallowed dry and washed down with a drink or mixed with water or milk Can be given via Nasogastric tube by mixing the powder in 10-20ml of water.	Hepatic Effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Although manufacturer does not recommend unless clearly necessary, animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. Lactation Where necessary can be used in breast-feeding.

Section 7.2: Lipid-soluble vitamins

Drug	Dose	Liver/Renal considerations	Pregnancy & Lactation
Vitamin BPC	2-4 capsules OD	<p>Hepatic effects Enhanced susceptibility to effects of vitamin A in hepatic impairment.</p> <p>Renal Impairment Use with caution in renal impairment.</p>	<p>Pregnancy Can be used during pregnancy.</p> <p>Lactation Can be used during breast-feeding.</p>
Vitamin A&D	2-3 capsules OD	<p>Hepatic effects Enhanced susceptibility to effects of Vit A in hepatic impairment</p> <p>Renal Impairment Use with caution in renal impairment.</p>	<p>Pregnancy Vitamin A&D capsules at RBH contain 450units of Vitamin D & 4500 units of Vitamin A. Maximum dose compatible with pregnancy and specifically CF patients is less than 10,000units/day of Vitamin A. Therefore maximum dose 2 Vitamin A&D capsules OD during pregnancy.</p> <p>Lactation Maximum dose of 2 capsules OD during breastfeeding.</p>
High dose Vitamin D (colecalciferol)	Refer to Trust Guidelines for Vitamin D in Adult CF pts	<p>Hepatic effects No dose adjustment in hepatic impairment</p> <p>Renal Impairment Use with caution in renal impairment.</p>	<p>Pregnancy Can use in pregnancy until maternal levels are normal. Plasma calcium and vitamin D levels must be regularly monitored to prevent hypercalcaemia. Limited data on high dose in pregnancy, however, evidence of deficiency during pregnancy has been associated with maternal and fetal complications such as pre-eclampsia, gestational diabetes, increase incidence of pre-term delivery, stillbirth and poor foetal bone development and growth retardation. High doses with normal levels of vitamin D, and hypercalcaemia can lead to complications.</p> <p>Lactation Limited concentrations enter into breast milk. Mothers deficient in Vitamin D may not provide sufficient levels to the infant & impede bone mineralisation. Excessive doses may lead to hypercalcaemia in the infant, therefore best to avoid in breast-feeding.</p>

Drug	Dose	Liver/Renal considerations	Pregnancy & Lactation
Vitamin E (Tocopheryl acetate) Vita E gel capsules	200iu (134mg) – 400iu (268mg) OD	Hepatic effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Safe in pregnancy. Lactation Can be used in breast-feeding at doses of no more than 400iu OD.
Vitamin K (Menadiol Diphosphate)	10mg OD PO	Hepatic effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Safe in pregnancy. Lactation Can use in breast-feeding.

Section 7.3: Gastro-oesophageal reflux

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Esomeprazole (2 nd line)	20 – 40mg OD	<p>Dose can be increased to maximum of 160mg daily in divided doses according to response in resistant cases or Zollinger-Ellison Syndrome</p> <p>Maximum single dose is 80mg. Doses greater than 80mg given in 2 divided doses.</p>	<p>Hepatic effects</p> <p>Severe hepatic impairment max. 20mg OD. In pts. <40kg with severe hepatic impairment max 10mg OD.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>Clinical data on exposed pregnancies are insufficient. Animal studies do not indicate direct or indirect harmful effects with respect to embryo/foetal development. The very limited published data do not suggest an increased risk of congenital malformations or other forms of foetal toxicity associated with the use during pregnancy. However, data is too limited to state that there is no increase in risk. Use with caution in pregnancy if treatment with alternatives which are known to be safe (such as omeprazole or ranitidine) cannot be used.</p> <p>Lactation</p> <p>It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed; therefore the manufacturer suggests that esomeprazole should not be used during breast-feeding. There have been, however, no reports found regarding neonatal toxicity following exposure to esomeprazole during lactation.</p>
Gaviscon® Advance	5-10mL as required after meals & at bedtime	<p>May damage enteric coatings designed to prevent dissolution in the stomach, therefore not to be used at the same time as E.C. preparations</p> <p>10ml contains 4.6mmol Na⁺ & 2mmol of K⁺. This should be taken in to account in patients on a salt restricted diet.</p>	<p>Hepatic effects</p> <p>No dose adjustment in hepatic impairment.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>Safe in pregnancy.</p> <p>Lactation</p> <p>Can be used during breast-feeding.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Lansoprazole (1 st line)	15-30mg OD	<p>Dose can be increased to max. 180mg daily according to response in resistant cases or Zollinger-Ellison Syndrome.</p> <p>Daily doses > 120mg given in 2 divided doses.</p> <p>FasTab tablet should be placed on the tongue & gently sucked.</p> <p>FasTab can also be dissolved in water & administered down NG tube or oral syringe.</p>	<p>Hepatic effects</p> <p>In pts with moderate or severe liver disease LFTs must be monitored regularly & max daily dose of 15-30mg given.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>Manufacturer advises avoid in pregnancy. Animal studies do not reveal any teratogenic effects, however, reproduction studies indicate slightly reduced litter survival and weights in rats and rabbits given very high doses of lansoprazole. Whilst limited published data do not suggest an increased risk of congenital malformations or other forms of foetal toxicity. However, data is too limited to state that there is no increase in risk.</p> <p>Lactation</p> <p>Avoid: there is no information on the secretion of lansoprazole into breast milk in humans.</p>
Omeprazole (1 st line)	<p>20- 40mg daily</p> <p>40mg OD IV (short term use only when oral route not possible)</p>	<p>Oral dose can be increased to 120mg daily according to response in resistant cases or Zollinger-Ellison Syndrome</p> <p>Max. single dose 80mg. Doses greater than 80mg given in 2 divided doses.</p> <p>IV administration:</p> <p>By slow IV bolus or IV infusion in 100ml N/S 0.9% or Glucose 5% over 15-30mins, depending on preparation & brand. Please check manufacturer's instruction or contact pharmacy for advice.</p> <p>MUPS/Dispersible tablets:</p> <p>Can be dispersed in water. Enteric coated pellets must not be chewed.</p>	<p>Hepatic effects</p> <p>In pts with hepatic impairment max daily oral & IV dose is 20mg.</p> <p>Monitor LFTs. If LFTs rise discontinue treatment.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy.</p> <p>Lactation</p> <p>Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used. Can be used in breastfeeding.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Pantoprazole (3 rd line)	20-40mg OD 40mg OD IV (short term use only when oral route not possible)	Oral dose can be increased to max. 160mg daily according to response in resistant cases or Zollinger-Ellison Syndrome Max. single dose 80mg. Doses greater than 80mg given in 2 divided doses. IV administration: By slow IV bolus or IV infusion in 100ml N/S 0.9% or Glucose 5% over 15-30mins.	Hepatic effects In severe hepatic impairment max. daily oral & IV dose is 20mg. Monitor LFTs. If LFTs rise discontinue treatment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity, therefore avoid in pregnancy. Lactation Animal studies have shown excretion in breast milk & excretion into human milk reported. Do not use in breast-feeding.
Ranitidine	150mg BD or 300mg ON	Oral dose can be increased to max. 300mg BD according to response in severe cases As per our practice at RBH – may be prescribed with PPI if needed as adjunct therapy.	Hepatic effects No dose change in hepatic impairment. Renal Impairment GFR 20-50ml/min dose as in normal renal function GFR 10-20ml/min dose as in normal renal function GFR <10ml/min 50-100% of normal dose.	Pregnancy Can be used in pregnancy. Documented experience in approximately 1500 exposed pregnancies. One study showed no increased risk of major malformations after 1 st trimester exposure. Other studies also argue against a teratogenic potential in humans. Considerable experience in late pregnancy, with no adverse neonatal effects attributed to ranitidine. Published data do not indicate that use of ranitidine is associated with an increased risk of congenital malformations or other adverse fetal effects. Lactation It is excreted in breast milk. Maternal ranitidine not expected to cause any adverse effects in breastfed infants. There were no reports found regarding neonatal toxicity following exposure to ranitidine during lactation.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Sucralfate (aluminium sucrose sulphate)	2g BD OM & ON PO or 1g QDS po1 hour before meals & at bedtime.	Maximum dose: 8g/day Avoid in patients receiving enteral feed or delayed gastric emptying due to risk of bezoar formation.	Hepatic effects No dose adjustment in hepatic impairment Renal Impairment GFR 20-50mL/min 4g daily GFR 10-20mL/min 2-4g daily GFR <10mL/min 2-4g daily	Pregnancy Absorption from GI tract negligible. Teratogenicity studies in mice, rats and rabbits at doses up to 50 times the human dose have revealed no evidence of harm to the foetus. Can be used in pregnancy. Lactation Minimal if any excretion in breast milk.

Section 7.4: Antiemetics

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Domperidone	10mg TDS PO (usual max 10mg TDS – increased doses may increase risk of cardiac adverse events).	Rare side effects include galactorrhoea, gynaecomastia, amenorrhoea and hyperprolactinaemia.	<p>Hepatic effects Despite manufacturers contraindicating its use, domperidone is the drug of choice in many liver centres as it has minimal side effects and can be used in all liver patients at usual starting dose 10mg TDS.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore avoid in pregnancy.</p> <p>Lactation It is excreted in breast milk of lactating rats. Concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations. It is not known whether this is harmful to the newborn. Breast-feeding is not recommended.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Levomepromazine	3mg-6mg or 3.125mg - 6.25mg ON PO or SC. Can be increased to 12.5mg -25mg BD according to response	Warn patients of pronounced sedative effects – may be negated by starting with small doses and titrating. Use higher doses at night if necessary.	Hepatic effects Avoid in hepatic impairment. Renal Impairment GFR 20-50mL/min dose as in normal renal function GFR 10-20mL/min dose as in normal renal function GFR <10mL/min start with small dose & increase as necessary.	Pregnancy Not recommended in pregnancy. Lactation Not recommended in breast-feeding.
Metoclopramide	10mg 8 hourly Po or IV bolus <40 kg: 5mg 8 hourly Po or IV bolus	Should be avoided in patients under 20yrs due to increased risk of extrapyramidal reactions involving facial and skeletal muscle spasms and oculogyric crises. Avoid in patients with epilepsy as frequency and severity of seizures may be increased. Use with caution after discussion with consultant due to risk of extrapyramidal side effects.	Hepatic effects Avoid in moderate to severe hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy No adverse foetal effects were reported in studies during 1 st & 2 nd trimester, with no significant risk of major malformations. No adverse birth outcomes in study of 309 women exposed in 1 st trimester. Has been used in all stages of pregnancy, no evidence of embryo, foetal, or newborn harm found in human and animal studies, so can be used. Lactation Metoclopramide is secreted into breast milk. Effects on newborn cannot be excluded. Adverse effects reported in 2 infants (mild intestinal discomfort), therefore avoid in breast-feeding.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ondansetron	<p>4-8mg 8 hourly PO or IV bolus</p> <p><40kg: 4mg 8 hourly PO or IV bolus</p>	<p>In patients. > 40kg additional PRN dosing may be given up to total maximum daily dose of 32mg.</p>	<p>Hepatic effects</p> <p>In patients with moderate to severe hepatic impairment the maximum daily dose is 8mg i.e 4mg 12 hourly.</p> <p>Renal Impairment (all levels) Dose as in normal renal function</p>	<p>Pregnancy</p> <p>Safety of ondansetron in human pregnancy has not been established. Experimental animal studies do not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and pre- and post-natal development. However, not recommended by manufacturer.</p> <p>Limited human data & animal reproductive studies show low risk of malformation. Where other anti-emetics have failed use of ondansetron may be considered. Has been used in pregnancy with no harmful effects.</p> <p>Lactation</p> <p>No reports on use in human lactation. Shown to pass into the milk of lactating animals, therefore not recommended in breast-feeding.</p>

Section 7.5: Treatment of constipation and Distal Intestinal Obstruction Syndrome (DIOS)

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Acetylcysteine 20% injection (oral & rectal)	Po: 30mL TDS in 150mL orange juice or water PR: 30mL added to phosphate enema TDS	Monitor electrolytes daily Acetylcysteine 20% Injection preparation used for PO/PR administration	Hepatic effects No dose change in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy It is not teratogenic or embryotoxic in experimental animals, although data is limited, does not appear to represent a risk to the foetus when given IV for paracetamol overdose. No reported pregnancy data on its use as a mucolytic. Lactation No reports in breastfeeding, although IV acetylcysteine has been administered to pre-term neonates at greater doses than would be obtained in breast milk without causing toxicity. Best to avoid breast-feeding.
Gastrografin® (oral & rectal)	50-100mL OD PO/PR with 200-400mL water	Due to Gastrografin® being very hypertonic patients must be well hydrated and advised to drink plenty of fluids. Where patients cannot take fluids orally then IV fluids should be given	Hepatic effects No information available on dose adjustments in hepatic impairment. Use with caution & monitor LFTs. Renal Impairment No information available on dose adjustments in renal impairment. Use with caution & monitor renal function as increased risk of worsening renal impairment.	Pregnancy Adequate and well-controlled studies in pregnant women have not been conducted. Animal studies do not indicate direct or indirect harmful effects with respect to embryo / foetal development. Caution should be exercised when using Gastrografin in pregnant women. Lactation Not known if excreted in breast milk, therefore avoid.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Klean-prep	Up to 4 sachets a day	Monitor electrolytes daily Do not give at bedtime due to risk of aspiration. Dissolve each sachet in 1 litre of water and drink within 1 hour. (The contents of all 4 sachets should be taken within 4-6 hours) If given via NG tube usual rate 20-30mL/min	Hepatic effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy Should only be used during pregnancy if considered essential by the physician. There is no experience of use during pregnancy. Not absorbed from gut, no teratogenic effects reported in pre-clinical studies, although no published studies on potential teratogenicity in human pregnancy. Lactation Avoid in breast-feeding.
Lactulose	15-20mL BD PO	Adjust dose according to response	Hepatic effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function.	Pregnancy Can be used in pregnancy. Lactation Can be used during breast-feeding.
Movicol®	1-3 sachets daily in divided doses PO	Monitor electrolytes May be increased to 8 sachets/day in divided doses Dissolve each sachet in 125ml water No more than 2 sachets should be taken in 1 hour.	Hepatic effects No dose adjustment in hepatic impairment. Renal Impairment (all levels) Dose as in normal renal function	Pregnancy There are no or limited data from use in pregnant women. Studies in animals have shown reproductive toxicity. Indirect embryofetal effects noted in rabbits. Not absorbed from gut, no teratogenic effects reported in pre-clinical studies, although no published studies on potential teratogenicity in human pregnancy, therefore only use if benefit outweighs risk. Lactation Can be used in breastfeeding.

Section 8 Bone Health

Section 8.1 Oral agents

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Alendronic acid (1 st line)	70mg once a week PO	<p>Due to risk of osteonecrosis of the jaw patients should maintain good oral hygiene, have routine dental checks & report any oral symptoms.</p> <p>Patients should be advised to report any thigh, hip or groin pain during treatment.</p> <p>Tablet must be taken at least 30 minutes before breakfast, any other drinks other than plain water & other medicines. Swallow whole with a full glass of water & sit or remain upright for at least 30minutes after taking.</p> <p>Counsel young women with respect to planning future pregnancies.</p>	<p>Hepatic effects No dose adjustment in hepatic impairment.</p> <p>Renal Impairment GFR 35-50mL/min Dose as in normal renal function GFR <35mL/min Avoid</p>	<p>Pregnancy</p> <p>Do not use in pregnancy: no adequate data from use in pregnant women. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcaemia.</p> <p>Lactation</p> <p>Do not use in breastfeeding.</p> <p>It is not known whether it is excreted into human breast milk.</p>

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Calcium and Vitamin D Preparations	Adcal-D3 (Chewable & Effervescent tablets) 1 tablet BD	Calcium 600mg (15mmol), colecalciferol 400 units (10mcg)/tablet Effervescent tablets should be dissolved in 200mL of water	Hepatic effects No dose adjustment in hepatic impairment. Renal Impairment GFR 10-50 mL/min Use with caution. GFR<10mL/min Avoid In patients with renal impairment monitor plasma phosphate, Ca ⁺² levels & urinary Ca ⁺² excretion & titrate dose according to plasma levels In patients with severe renal insufficiency, colecalciferol is not metabolised in the normal way and alternative forms of vitamin D must be used.	Pregnancy Vitamin D deficiency has been associated with maternal & foetal complications such as pre-eclampsia, gestational diabetes, increase incidence of pre-term delivery, stillbirth and poor foetal bone development & growth retardation. Can use in pregnancy but maternal plasma calcium levels must be monitored. Lactation Vitamin D and its metabolites pass into the breast milk. Can be used in breastfeeding but monitor plasma calcium levels.
	Cacit D3 Granules 1-2 sachets daily	Calcium 500mg (12.5mmol), colecalciferol 440 units (11mcg)/tablet Dissolve sachet in large glass of water		
	Calceos Chewable tablets 1 tablet BD	Calcium 500mg (12.5mmol), colecalciferol 400 units (10mcg)/tablet		
	Calcichew D3 1 tablet BD - TDS	Calcium 500mg (12.5mmol), colecalciferol 200 units (5mcg)/tablet Chew or suck tablet		
	Calcichew D3 Forte/Calcichew D3 Caplet 1 tablet BD	Calcium 500mg (12.5mmol), colecalciferol 400 units (10mcg)/tablet Caplets may be swallowed – Forte tablets suck/chew		

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Risedronate (2 nd line)	35mg once a week PO	As for alendronate (see notes above)	<p>Hepatic effects No dose adjustment in hepatic impairment.</p> <p>Renal Impairment GFR >20mL/min: Dose as in normal renal function GFR < 20mL/min: Avoid</p>	<p>Pregnancy No adequate data from use in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Do not use in pregnancy.</p> <p>Lactation Do not use in breast-feeding Studies in animals indicate that a small amount of risedronate sodium pass into breast milk.</p>
Strontium Ranelate (sachet)	2g OD PO	<p>Life-threatening cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms have been reported. Patients should be advised of the signs and symptoms & monitored closely for skin reactions. The highest risk for occurrence is within the first weeks of treatment (3-6 weeks)</p> <p>Absorption reduced by food & milk, therefore avoid food for 2 hours after taking</p> <p>Dissolve sachet in at least 30mL water.</p>	<p>Hepatic effects No dose adjustment in hepatic impairment.</p> <p>Renal Impairment GFR >30mL/min: Dose as in normal renal function GFR <30 mL/min: Avoid.</p>	<p>Pregnancy Do not use in pregnancy.</p> <p>Lactation Do not use in breast-feeding. Expected to cross in to breast milk.</p>

Section 8.2 Other agents

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ibandronic acid injection	3mg every 3 months	<p>Use when oral treatment not tolerated or effective or on advice of consultant endocrinologist.</p> <p>Administer by slow IV bolus.</p> <p>If dose is missed should be given asap & 3 monthly thereafter.</p> <p>Due to risk of osteonecrosis of the jaw patients. should maintain good oral hygiene, have routine dental checks & report any oral symptoms.</p> <p>Patients should be advised to report any thigh, hip or groin pain during treatment.</p> <p>Counsel young women with respect to planning future pregnancies.</p>	<p>Hepatic effects No dose adjustment in hepatic impairment.</p> <p>Renal Impairment GFR >30mL/min: Dose as in normal renal function GFR < 30mL/min. Avoid</p>	<p>Pregnancy Do not use in pregnancy. No reports on use in pregnancy. Animal studies showed reproductive toxicity. Theoretical risk of harm to foetus e.g. skeletal and other abnormalities.</p> <p>Lactation Do not use in breast-feeding. No reports of ibandronic acid use in breastfeeding.</p>
Teriparatide (Last line on consultant endocrinologist decision only)	20mcg OD SC injection	<p>Inject by SC injection in thigh or abdomen</p> <p>Maximum duration of treatment is 24 months</p>	<p>Hepatic effects Use with caution in hepatic impairment.</p> <p>Renal Impairment Use with caution in moderate renal impairment. Avoid in severe renal impairment.</p>	<p>Pregnancy Do not use in pregnancy. Studies in rabbits have shown reproductive toxicity. Effect on human foetal development has not been studied. Potential risk for humans is unknown.</p> <p>Lactation Do not use in breast-feeding. Not known whether excreted in human milk.</p>

Section 9 Haemoptysis

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Terlipressin	Initially 2mg then 1-2mg every 4-6 hours until bleeding is controlled, (maximum duration 72 hours).	As terlipressin has antidiuretic and pressor activity it should be used with great caution in patients with hypertension, atherosclerosis, cardiac dysrhythmias or coronary insufficiency. Constant monitoring of blood pressure, serum sodium and potassium and fluid balance is essential.	Hepatic Impairment A dose adjustment is not required in patients with liver failure. Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function. Use with caution. GFR <10mL/min Dose as in normal renal function. Use with caution.	Pregnancy Not recommended by manufacturer, however, benefit may outweigh risk in clinical situation where this is required. Lactation No information available. Manufacturer advises avoid.
Tranexamic Acid	PO: 500mg – 1g every 8 hours		Hepatic Impairment No specific dose reduction recommended. Renal Impairment GFR 20-50mL/min IV: 10mg/kg 12 hourly. Oral: 25mg/kg 12 hourly GFR 10-20mL/min IV: 10mg/kg 12-24 hourly. Oral: 25mg/kg 12-24 hourly. GFR <10mL/min IV: 5mg/kg 12-24 hourly. Oral: 12.5mg/kg 12-24 hourly	Pregnancy No adverse effects attributed to use during pregnancy in humans. Limited amount of data available at present does not support an association between the use of tranexamic acid during pregnancy and an increased risk of venous thrombosis. If use of tranexamic acid is indicated in the treatment of maternal illness treatment should not be withheld on account of pregnancy. Lactation Tranexamic acid passes into breast milk - an antifibrinolytic effect in the infant is unlikely.
	IV: 500mg – 1g every 8 hours ^{viii}			

Section 10 CF Related Liver Disease

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ursodeoxycholic Acid	<p>20mg/kg/day in 2 – 3 divided doses^{ix} (we usually dose BD).</p> <p>The dose may need to be increased gradually to target dose to avoid adverse effects.</p>	Improvement of hepatic metabolism of essential fatty acids and bile flow	<p>Hepatic effects No dose adjustment in hepatic impairment.</p> <p>Renal Impairment (all levels) Dose as in normal renal function.</p>	<p>Pregnancy Animal studies have not shown direct teratogenic effects when administered to pregnant rats, mice & rabbits. Use in treatment of intrahepatic cholestasis of pregnancy appears to be low risk for the foetus. Data in 1st trimester is extremely limited & lacking, although the limited data available has not shown an increased risk of congenital malformations. Use in later pregnancy 2nd & 3rd trimester have not shown any adverse foetal outcome. Only use if benefit outweighs the risk.</p> <p>Lactation No reports of use during lactation. Avoid in breast-feeding.</p>

Section 11 Immunomodulators

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Azithromycin	<p>< 40 kg: 250 mg three times a week > 40 kg: 500 mg three times a week <i>Usually Monday, Wednesday and Friday</i></p> <p>Alternative dose: 250 mg OD to aid adherence or to reduce GI side effects; Dose can be increased to 500mg OD if deterioration, on consultant's decision</p>	<p>Long-term benefits independent of microbiology: for immuno-modulatory effect.</p> <p>Patients should be advised to stop azithromycin treatment and seek advice if they experience any changes in their hearing such as tinnitus.</p> <p>Avoid single agent treatment with a macrolide in patients who have grown <i>M. abscessus</i> or <i>M. avium</i> due to risk of emergent resistance with unopposed macrolides.</p> <p>Patients prescribed long term azithromycin should have baseline ECG to identify QTc prolongation. Use with caution if QTc prolonged. Repeat at annual review.</p>	<p>Hepatic effects Check liver function 1 month after commencing continuous azithromycin therapy.</p> <p>No dose adjustments are needed in mild to moderate liver impairment; monitor LFTs. Avoid in severe liver disease.</p> <p>Renal Impairment GFR 20-50mL/min Dose as in normal renal function GFR 10-20mL/min Dose as in normal renal function GFR <10mL/min Caution due to 33% increase in systemic exposure to azithromycin.</p>	<p>Pregnancy Not associated with an increased risk of malformations or adverse pregnancy outcome.</p> <p>Lactation Because of the low levels of azithromycin in breast milk and use in infants in higher doses, it would not be expected to cause adverse effects in breastfed infants. Monitor for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis.</p>

Section 12 CFTR Modifying Drugs

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy and Lactation
Ivacaftor	Patients with confirmed G551D CFTR mutation: 150mg BD	<p>All patients must have had a sweat chloride test within the 6 months prior to starting treatment and be informed of the stopping criteria at the time of starting treatment with ivacaftor (see specialised commissioning policy: 'Ivacaftor for Cystic Fibrosis.')</p> <p>Refer to RBH 'Guidelines for the use of ivacaftor in adult and paediatric patients with cystic fibrosis.'</p> <p>Ivacaftor should be taken with a fat-containing meal.</p> <p>Liver function tests are recommended prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter.</p> <p>When co-administered with potent inhibitors of cytochrome p450 isoenzyme CYP3A (such as itraconazole, posaconazole, voriconazole, clarithromycin), reduce dose of ivacaftor to 150mg twice weekly.</p> <p>When co-administered with moderate inhibitors of CYP3A (such as fluconazole, erythromycin), reduce dose of ivacaftor to 150mg once daily.</p>	<p>Hepatic effects</p> <p>Mild hepatic impairment (Child-Pugh A): No dose adjustment necessary.</p> <p>Moderate hepatic impairment (Child-Pugh B): Reduce dose to 150mg once daily</p> <p>Severe impairment (Child-Pugh C): No clinical experience – if benefits outweigh risk consider starting dose 150mg once daily on alternate days and adjust according to response and tolerability.</p> <p>Renal Impairment</p> <p>GFR >30mL/min No dose adjustment necessary.</p> <p>GFR ≤30mL/min Negligible urinary excretion, however, manufacturer advises caution: adjust dose if necessary according to response/tolerability.</p>	<p>Pregnancy</p> <p>No information available in human pregnancy. Developmental toxicity studies have been performed in rats and rabbits at daily doses up to 5 times the human daily dose and have revealed no evidence of harm to the foetus due to ivacaftor. Because animal reproduction studies are not always predictive of human response, Kalydeco should be used during pregnancy only if clearly needed.</p> <p>Lactation</p> <p>The safe use of ivacaftor during breast-feeding has not been established: it is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Ivacaftor was shown to be excreted into the milk of lactating female rats; however, in humans, ivacaftor is highly protein bound (99%). Drugs that are highly protein bound are less likely to pass from the bloodstream into breast milk. Continue if potential benefits outweigh any potential risks.</p>
