Clinical Guidelines: Care of Children with Cystic Fibrosis

Royal Brompton Hospital

Royal Brompton & Harefield NHS
NHS Foundation Trust

Available on –
www.rbht.nhs.uk/childrencf

2011

5th edition

The 5th edition of these guidelines has been written by members of the Royal Brompton Hospital Paediatric Cystic Fibrosis Team. Contributors over the years include:

Saji Alexander, Khalid Alshafi, Ian Balfour-Lynn, Roger Buchdahl, Fran Beresford, Cara Bossley, Nicola Bridges, Sarah Brown, Andrew Bush, Nicola Collins, Christina Courtney, Jacqui Cowlard, Finella Craig, Jane Davies, Katie Dick, Emma Dixon, Siân Edwards, Sarah Elkin, Amanda Equi, Jackie Francis, Frances Goodhart, Alex Handford, Jonny Harcourt, Tom Hilliard, Nicola Hirsch, Sam Irving, Mary Jurd, Wanda Kozlowska, Su Madge, Sukeshi Makhecha, Angela McCullogh, Andrea McKee, Donna McShane, Caro Minasian, Adam North, Caroline Pao, Sarah Pike, Michèle Puckey, Lucy Reed, Mark Rosenthal, Vikki Stone, Pat Stringer, & Rivanna Stuhler.

2nd to 5th editions were edited by Dr Ian Balfour-Lynn.
1st edition (1994) was edited by Dr Pat Oades.

These guidelines are based on published evidence as well as the extensive clinical experience of our Paediatric 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 we anticipate that patients, who come to the Royal Brompton Hospital, either for full or shared care, will be looked after using these guidelines.

These guidelines have been endorsed by the Medicines Management Board of Royal Brompton & Harefield NHS Trust.

If there are any comments, queries or errors noticed, please contact Ian Balfour-Lynn on i.balfourlynn@ic.ac.uk.

Next revision will be 2013 so this edition should not be used from 2014. Please destroy all 2007 editions.

What's new in the 5th edition?

There are several changes and updates throughout this guideline but these are the principal ones (section numbers in brackets).

New personnel & contact numbers: (2)

New sections
- Newborn screening (5.4);
- Mannitol (6.6);
- Challenging CF protocol (6.12);
- Non-invasive positive pressure ventilation (6.16).

Additional information
- PortCF (3.2);
- Family liaison team (3.7);
- Extended genotype analysis (5.4);
- Pre-implantation genetic diagnosis referrals (5.4);
- Epipens for home IVABs (6,2b);
- Transplant referral proforma (9).

New appendices
- Treatment of non-tuberculous mycobacteria (II);
- Antibiotic protocol for newborn screened babies in the Early Detection of Lung Disease Study (III);
- Tables for body surface area (V);
- GP shared care documents for Bramitob / TOBI (VIII), and colomycin (IX).
- Gene mutation nomenclature (XI)

New drugs
- AZLI (nebulised aztreonam);
- Bramitob (nebulised tobramycin);
- Inhaled mannitol.
- IV caspofungin

Policy changes / additions:
- Bone densitometry (DEXA) scans to be measured alternate years in everyone aged 8 years and above at annual review (3.2);
- Liver ultrasounds to be done alternate years in all patients aged 5 years and above at annual review; they will be done without fasting so gall bladder will not be well visualised (3.2);
- Lung clearance index measured at annual reviews (3.2);
- Re-instigate measurement of vitamin D at annual review, stop measuring IgA & IgM (3.2);
- In-patients will have annual reviews on day 3 (bloods) and day 10 (other measures) (3.2);
- Chest x-rays are no longer scored, but record changes and differences from last year (3.2);
- Transition clinic visits at 15 and 16 years (3.3);
- When having IV colomycin, monitoring of electrolytes weekly (not twice weekly) unless on other nephrotoxic drugs (4.2);
- When on oral chloramphenicol full blood count now 3 weekly not 2 weekly (4.2);

- Sedation policy and use of Entonox (4.3);
- Advice for mothers on subsequent pregnancy (5.4);
- Clinic letters must state date of last *P. aeruginosa* isolation and whether mucoid (6.2a);
- Oral ciprofloxacin for 3 weeks (not 2) for 1st isolation *P. aeruginosa* (6.2a);
- We no longer routinely use nebulised gentamicin unless there are also significant problems with *S aureus* or perhaps the 1st isolation is mucoid and resistant. Colomycin is given at double previously stated doses (6.2a);
- 1st *P. aeruginosa* in newborn screened child before initial surveillance bronchoscopy will be treated with IV antibiotics started at time of bronchoscopy. If picked up on BAL only we will also use IV antibiotics, but will repeat bronchoscopy after 3 months of nebulisers to see if eradicated (6.2a);
- Failure of eradication of 1st isolation *P. aeruginosa* ie, cultured after 3 months colomycin treatment, may be an indication for IV antibiotics or nebulised tobramycin (6.2a);
- 1st isolation MRSA in sputum/cough swab is treated for 3 months with rifampicin plus fusidic acid (or trimethoprim as alternate 2nd agent) (6.2a);
- Routine culture for NTM at annual review, but also now in a child who is suboptimal and culture-negative on routine microbiology, in bronchoalveolar lavage, and also when admitted for an exacerbation, and when previously cultured (6.2a);
- Doxycycline may be used as an alternative to minocycline as it is once daily, although minocycline is still part of the NTM protocol; minocycline MR (once daily modified release) also available (6.2a);
- IV gentamicin is not used and is removed as an option (6.2a);
- Tobramycin levels to be taken 23 hours after 1st dose. Ideally tobramycin given at 2 pm (6.2a);
- Use of Bramitob as first line nebulised tobramycin solution (6.2a);
- Use of nebulised AZLI (6.2a);
- Competency booklet for parents doing home IVABs (6.2b);
- The threshold for starting DNase is lowered and we expect patients to have it if their FEV_1 is <85%. Additionally, a child aged 6 years and above should have it if they are having recurrent respiratory symptoms, whatever their lung function. Starting it is a consultant decision (6.4);
- DNase still preferred at tea time (1 hour before physio), but can be given before bedtime in some individuals (6.4);
- Use of inhaled mannitol (6.6);
- When long term azithromycin is started, prophylactic flucloxacillin is continued; but prophylactic augmentin may be stopped (unless the patient is known to have macrolide-resistant *H influenzae*) (6.7)
- Use of IV methylprednisolone in ABPA (6.8);
- Measurement of itraconazole and voriconazole levels (6.8);
- Itraconazole given twice daily ie, double previous dose (6.8);
- Consideration of omalizumab (6.8);
- Challenging CF protocol (6.12);
- A cough swab / sputum sample must be taken on the same day prior to a bronchoscopy (6.13);
- Using updated UK-WHO 2009 growth charts for new patients (7.1);
- Pancrease has been discontinued (7.2);
- Coeliac screen now consists of anti-gliadin IgG & IgA; and TTG (anti tissue transglutaminse) (7.3);
- Use of continuous glucose monitoring system - CGMS (8.1);
- Use of non-fasting OGTT as 1st line (8.1);

- Only those with severe lung disease should routinely have intravenous antibiotics prior to surgery (10.1);
- H1N1 influenza immunisation (10.2);
- Varicella antibodies to be checked at 6th birthday annual review (and catch up of older children in 2011). If negative, we will offer immunisation (10.3).

Formulary

Additions	*Changes*
• Nebulised amikacin • Nebulised AZLI (aztreonam) • Nebulised Bramitob (tobramycin) • Nebulised meropenem • Nebusal solution for 7% hypertonic saline • Oral ethambutol • IV caspofungin • IV teicoplanin • IV temocillin • IV tigecycline, • Inhaled mannitol	• Deleted tobramycin IV solution for nebulisation • Deleted oral flucytosine • Deleted oral cefixime • Deleted oral cefaclor • Deleted IV gentamicin • Increase itraconazole dose • Augmentin Tablet doses for 6 yrs and above • IV tobramycin 10 mg/kg od (instead of 10-12).

Contents

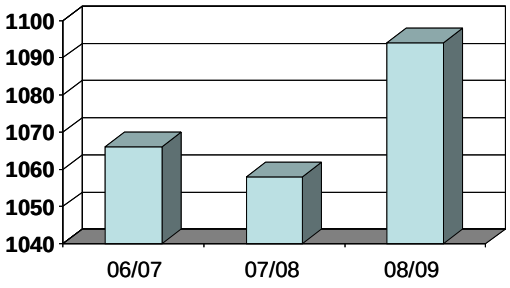
1. Introduction

The purpose of this document is to set out guidelines to ensure standardised care for children with cystic fibrosis looked after at the Royal Brompton & Harefield NHS Foundation Trust and District General Hospitals on a shared care basis. They should be used as a guide only. The Royal Brompton Hospital is a Specialist CF Centre as defined by the CF Trust Clinical Standards & Accreditation Group.

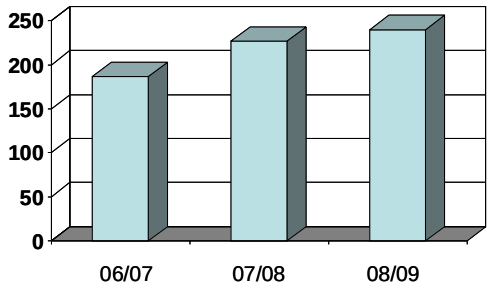
Our philosophy of care for patients with cystic fibrosis is based on current guidelines laid down by the Royal College of Physicians, Royal College of Paediatrics & Child Health (formerly British Paediatric Association), CF Trust and the British Thoracic Society. These have identified significant advantages in terms of survival and morbidity for patients receiving care from specialist centres. Specialist centres offer access to comprehensive care from a multidisciplinary team consisting of consultants with a special interest in CF, junior doctors, nurse specialist, dietitian, physiotherapist, clinical psychologist, pharmacist and social worker. The team is also responsible for producing and distributing educational material and carrying out research to improve knowledge about this disease. Special procedures and investigations are provided that may not be available at District General Hospital level (such as formal lung function and bronchoscopy). It is not our aim to monopolise patient care. We prefer to establish a shared care policy, so that patients remain primarily under the care of their local consultant. We also have established a number of out-reach clinics whereby our consultants see CF patients in their local hospitals.

Death in childhood from CF is now rare, and children born today are likely to have a mean life expectancy of over 40-50 years. There are approximately 8500 people with CF in the UK and just under half are children. On average, large District General Hospitals will have a local CF population of between 10 and 20 patients and General Practitioners between 0 and 2 patients. The Paediatric Clinic at the Royal Brompton Hospital has around 320 children under its care whilst there are about 600 patients in the Adult Clinic. The paediatric team normally sees children and adolescents until they leave school or until the children wish to be transferred to the adult team. Follow-up is then offered in the adult clinic at the Royal Brompton Hospital.

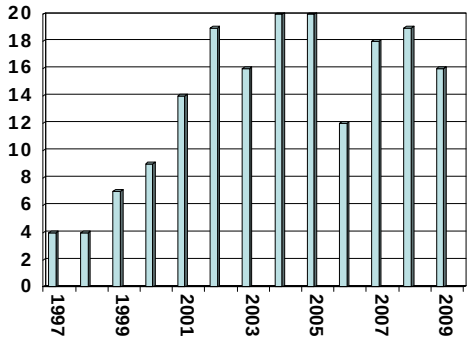
Out-patient visits



In-patient stays



Research publications from Paediatric CF Unit



2. Department staff and contact numbers

Department of Paediatric Respiratory Medicine
Royal Brompton & Harefield NHS Trust
Sydney Street,
London, SW3 6NP

☎ 0207-352 8121
Fax: 0207-351 8763

Prof Andrew Bush	Professor & Honorary Consultant in Paediatric Respiratory Medicine a.bush@rbht.nhs.uk
Dr Mark Rosenthal	Consultant in Paediatric Respiratory Medicine m.rosenthal@rbht.nhs.uk
Dr Ian Balfour-Lynn	Consultant in Paediatric Respiratory Medicine i.balfourlynn@ic.ac.uk
Dr Jane Davies	Reader & Honorary Consultant in Paediatric Respiratory Medicine j.c.davies@imperial.ac.uk
Dr Claire Hogg	Consultant in Paediatric Respiratory Medicine (in-patient care only for CF) c.hogg@rbht.nhs.uk
Dr Sejal Saglani	Senior Lecturer and Honorary Consultant in Paediatric Respiratory Medicine (in-patient care only for CF) s.saglani@rbht.nhs.uk
Dr Caro Misanian	Consultant in Paediatric General & Respiratory Medicine (2 clinics per month)
Dr Richard Chavasse	Consultant in Paediatric Respiratory Medicine (2 clinics per month)
Dr Catherine Greenaway	Consultant in Paediatric General & Respiratory Medicine (2 clinics per month)

CF Secretary 0207-351 8674; Fax 0207-351 8763

Consultant secretaries	Extension	0207-351 8232 (Bush) 0207-351 8754 (Rosenthal) 0207-351 8509 (Balfour-Lynn) 0207-351 8509 (Davies)

Paediatric CF Nurse – Specialists	**Jackie Francis** (Hospital care) Bleep1213, Ext 8755 Direct line / answerphone 0207-351 8755 j.francis@rbht.nhs.uk
	Pat Stringer (Home care) Mobile Phone 07973 173 969
	Katie Dick (Hospital & home care) Mobile Phone 07971 224 068
	Karen Henney (Hospital & home care) Mobile phone 07971 224 068
Adult CF Nurse Consultant -	**Dr Su Madge** Bleep 7032, Ext 4053
Specialist Registrars -	Bleep on-call SpR (Respiratory paediatrics) via Hospital Switchboard – bleep 1237
Physiotherapy -	**Nicola Collins** Bleep 7304, Extension 8088
Home care physiotherapy -	**Emma Dixon** 07970 269 452
	Nicky Murray 07791584749
Dietitian –	**Mary Jurd** **Caroline Smith** Bleep 7101, Ext 8465
Clinical psychologists –	**Michèle Puckey** 0207 3528121 Ext 4130/Bleep 1228 (Mon to Fri)
	Dr Frances Beresford 020 7352 8121 Ext 4131 Bleep 1263 (Tues & Fri)
	Locum 020 73528121 Ext 4131 Bleep 7053

Pharmacists	**Siân Edwards** Extension 4375, Bleep 7403
	Adam North Extension 4375, Bleep 7410
Family Liaison Service (Rose Ward)	**Jane Docker** Extension 8588, Bleep 1274
	Sarah Worboys Extension 8588, Bleep 1250
Social worker –	**Alex Handford** 0208 846 1179 Bleep 7552 Extension 8060 07973 564580
Wards	Paediatric Ward - Rose Gallery Direct line - 0207 351 8588, Extensions 2411, 2412, 2413
	Adult Ward - Foulis Extensions 8069, 4070, 4868

The above can usually be contacted between 9am and 6 pm. Non-urgent messages can be left on the answerphone of the CF Nurse Specialist (0207-351 8755) or the consultant secretaries. For urgent problems, please phone hospital switchboard (0207-352 8121) and ask for the on-call paediatric respiratory SpR.

Referrals to other specialists

At times we request other consultants to see the children, and this is often done in conjunction with the shared-care consultants. SpRs must not make referrals without prior discussion with Brompton consultant. Our own practice is to use the following:

Dermatology	Dr Nerys Roberts	Chelsea & Westminster Hospital
Ear Nose and Throat	Mr Will Grant	Chelsea & Westminster Hospital
	Mr Jonny Harcourt	Chelsea & Westminster Hospital
	Mr Guri Sandhu	Chelsea & Westminster Hospital
Gastroenterology	Dr Jenny Epstein	Chelsea & Westminster Hospital
	Dr John Fell	Chelsea & Westminster Hospital
Genetics	Dr Sue Holder	Kennedy Galton Centre
Diabetes / growth / puberty	Dr Nicola Bridges	Chelsea & Westminster Hospital
Diabetes	Dr Saji Alexander	Chelsea & Westminster Hospital

Gynaecologist	Mr Guy Thorpe-Beeston	Chelsea & Westminster Hospital
	Ms Jane Bridges	Chelsea & Westminster Hospital
Heart-lung Transplant	Dr Helen Spencer	Great Ormond Street Hospital
Hepatology	Dr Marianne Samyn	King's College Hospital
Paediatric Surgery	Mr Simon Clarke	Chelsea & Westminster Hospital
	Mr Muntha Haddad	Chelsea & Westminster Hospital
Radiology	Prof David Hansell	Royal Brompton Hospital
Rheumatology	Dr Clarissa Pilkington	Great Ormond Street Hospital
Thoracic Surgery	Mr Michael Dusmet	Royal Brompton Hospital
	Mr Simon Jordan	Royal Brompton Hospital
	Mr Eric Lim	Royal Brompton Hospital

3. How the service runs

3.1 Clinics

The clinics are run in a segregation format (see section 4.6). There are 2 clinics per week, Monday and Friday 1:30pm to 5:00pm (4.15 is last appointment). In addition, new patients are occasionally seen in a general respiratory clinic on Tuesdays or Wednesdays 2-5pm. Patients infected with *B cepacia* complex (and who have not yet had 1 year of clear cultures) are also seen in the general respiratory clinics (Tues or Wed). Patients may attend either clinic at their convenience. Most children are seen in a CF clinic every 2 months, or every 3 months for those recognised to have mild disease. For some, all clinic visits are at the Royal Brompton Hospital, whilst others are seen on a shared-care basis with a local District General Hospital, usually on alternative visits. We aim for all patients to be seen at Brompton 6 monthly minimum but there are a few patients who are seen yearly only at RBH for annual review (they live abroad). All out-patient visits are discussed at a weekly multi-disciplinary meeting at which the consultants are present. After every clinic visit, a letter is sent to the GP, shared-care consultant and parents, which is countersigned by one of the consultants.

The families see the following:

Doctor. This may be a consultant (Mondays – Prof Bush, Drs Davies & Chavasse / Fridays – Drs Rosenthal, Balfour-Lynn & Minasian, a specialist registrar (usually a national grid respiratory trainee), or a respiratory clinical/research fellow. Parents may request which doctor they wish to see, and this is usually possible although may lead to a longer waiting time.

All patients are allocated a **named consultant** when first seen at our unit**,** although may be seen by any member of the consultant team at various times. The named consultant will take the lead role if there are difficult clinical decisions to be made. They will also co-sign all clinic letters and write the annual review reports.

Health Care Assistant. To measure height and weight.

Respiratory technician. To measure lung function.

CF nurse specialist. Jackie Francis sees all patients and provides general information and support. When she is unavailable one of the other CF nurses will be in clinic.

Physiotherapist. All the children should be seen by a physiotherapist to review techniques, and to obtain sputum or cough swab specimens, or a nasopharyngeal aspirate. This is usually in one of the clinic rooms, but sometimes the children are seen in the Physiotherapy Department.

Dietitian. Most patients are seen by the dietitian, particularly if there is a problem with their nutrition and weight gain. It may not be necessary to see her at every clinic visit.

Others. In addition, if there is a particular problem, the families may also see one of our clinical psychologists or our social worker, although often separate appointments are made. The social worker or Welfare Rights Officer can often help with guiding parents on how to

obtain appropriate benefits to which they are entitled. The paediatric pharmacy team can be contacted via bleep for medication related enquiries.

Clinic procedures

- Children are always weighed (in underwear) and have their height measured on a stadiometer. Head circumference should be measured in children less than 1 year of age.
- Children over 5 years have lung function measured on a standard spirometer. All children have oxygen saturation measured on a pulse oximeter.
- Urine is tested for glucose if the child has lost weight or if they are receiving oral steroids, in which case blood pressure is also measured.
- Sputum or cough swabs are always collected for microbiology. Have a low threshold for culturing for NTM as well, especially if the child is sub-optimal and results usually show no growth.

Research
Always consider whether the child might be suitable for one of our research projects.

3.2 Annual review

All patients are seen around the time of their birthday for a full clinical review of progress over the last year, which takes place in the normal CF Clinic. If someone is an in-patient around that time, their annual review (A/R) will take place during the admission (usually bloods on day 2 with aminoglycoside levels, and other measures e.g. chest x-ray & formal lung function on day 9-10). The SpRs must fill in the PortCF proforma so that an entry is made on to the PortCF database. In addition for those having regular admissions, bloods will always be taken for annual review so that they do not need repeating in clinic.

The results and whole clinical picture are then reviewed by the named consultant, who will decide on any management changes. The medical input in clinic would usually be from the CF Fellow or Clinical SpR, with certain exceptions. Children who are seen regularly at the Brompton or in peripheral clinics will be seen by a consultant two months later in either clinic. For those few children who are seen once yearly only, the initial review is carried out by the consultant whenever possible. Occasionally, at the end of the annual review initial visit (done by SpR), the consultant will come in to see them as well for a brief discussion. All families will receive the Consultant's opinions & summary of review by letter once results are known. The children will be seen for the following:

- Discussion with and examination by one of the clinic doctors following the PortCF proforma. This will include the number of IV and oral antibiotic courses, usual symptoms and microbiology. There will also be an emphasis on growth and puberty. The doctor will also ensure that the issue of fertility has been discussed with children at the appropriate age (section 8.7). The doctor will discuss results of lung function (or ventilation scan) and chest x-ray. The CF Trust Database forms are also filled in which is mandatory in order to put full data onto PortCF.

- Discussion with CF nurse specialist.
- Dietary assessment - including written evaluation of nutritional intake by the dietitian. Height & weight, growth velocity and BMI charts will be filled in.

- Physiotherapy review of airway clearance techniques, exercise and inhaled medication regimens. Posture and urinary stress incontinence will be reviewed when appropriate. Home air compressors for nebulisation should be brought in for yearly service. Parents must contact the Physiotherapy Department to book an appointment for servicing on 0207 351 8088, when they have the date for their review. Exercise testing is not routinely carried out.

- When possible, the families will meet one of the clinical psychologists for an informal discussion. They will be able to ascertain whether there are any issues the families wish to discuss in more detail and arrange a suitable follow-up appointment. We aim to use a screening questionnaire when staffing levels allow. If the families are already involved with one of our psychologists, then they will not need to be seen at annual review unless they wish to make an appointment in advance.

Investigations

- *Full lung function* (including plethysmography) for children over 6 years. Bronchodilator responsiveness will be carried out for specific patients only by request. This is done in the Lung Function Laboratory on the 1st floor Fulham wing and takes 1 hour.

- *Lung clearance Index (LCI)*. This test requires only passive co-operation, and can potentially be performed at all ages. The child breathes normally through a mask or mouthpiece while a low concentration of an inert gas (usually sulphur hexafluoride, SF_6) is inhaled. After equilibration, the SF_6 source is disconnected and the concentration of gas in the exhaled air is monitored. LCI is calculated from the number of total lung volumes turnovers required to wash out SF_6 to $1/40^{th}$ of the original concentration.

  The advantages of the test include (a) it is non-invasive, (b) only passive co-operation is needed, (c) the normal value is essentially the same over the whole age range, (d) it is more sensitive than spirometry to early disease. It is also frequently used as a research technique. If a child has grossly abnormal obstructive spirometry, the test will take a long time and be tiring for the child. It is also not likely to add much useful information, so discuss with a Consultant first.

  Subject to the above, LCI should be a routine part of the annual assessment (currently for all aged 12 and above). Additionally, the test is particularly useful in children who supposedly have 'poor technique' with spirometry, and we can measure it in children as young as 4-5 years old. Whilst this may be true, equally it may mask the fact that their lung function is genuinely low. LCI should be booked through Sam Irving (ext. 8233, email s.irving@rbht.nhs.uk) and is carried out in Chelsea Wing level 4.

  The higher the LCI, the worse is the distal gas mixing. A **normal value is < 7.1**, and a significantly abnormal level is above 10 (we have not had values >12).

- *Ventilation scan* is carried out in children too young to perform formal lung function. This is done in Nuclear Medicine Department, Level 3 Chelsea Wing and takes 1 hour. Ext 8666.

- *Chest x-ray* is no longer scored but we record changes and differences from the last year.

- *Ultrasound liver and spleen*. Liver ultrasound will be performed as screening at the Brompton Hospital (or at the local hospital) on all children aged 5 years and above every other year (e.g. age 5, 7, 9, 11, 13, 15 yrs). It should be performed in the meanwhile in anybody with a palpable liver/spleen or significantly abnormal liver function test (2x upper limit of normal). If the ultrasound is abnormal or there are other liver abnormalities (hepatosplenomegaly, blood results) it will be repeated annually. It will be done without the child fasting for convenience. The only downside of that is that is the gall-bladder will not be visualised well. This will not matter unless the child is having abdominal pain in which case it is important to look for biliary stones.

- *Bone densitometry (DEXA scan)* is to be measured every other year as screening in all children aged 8 years and over (e.g. aged 8, 10, 12, 14, 16 years). It is particularly important they are measured in patients considered to be at increased risk of developing reduced bone density (section 8.3). These would include those who have frequent oral steroids (particularly those with chronic ABPA), those on high dose inhaled corticosteroids, anyone receiving insulin and those with FEV_1<50% predicted. Ext 8965. If abnormal, it will be repeated annually.

- *Oral glucose tolerance tests* are not done routinely in all patients, but in some patients at increased risk of developing CF-related diabetes they should be considered at annual review. We may decide to carry out CGMS (continuous glucose monitoring system) in some patients. See section 8.1.

- *Sputum or cough swab* for microbiology including non-tuberculous mycobacteria.

- *Blood* is taken by the phlebotomist (or doctor). 15 ml is taken for the following:
    - Full blood count (with WBC differential)
    - Clotting studies
    - Electrolytes and creatinine
    - C-reactive protein
    - Calcium, magnesium and phosphate
    - Liver function tests (AST, ALT, ALP, γGT)
    - Random glucose and glycosylated Hb
    - Vitamins A, D & E
    - Serum iron, ferritin and TIBC
    - IgG
    - IgE
    - Aspergillus RAST (specific IgE)
    - Aspergillus IgG (ICAP)

Blood bottles: 3 (red) EDTA bottles, 6 (brown) SERUM bottles,1 (green) COAGULATION bottle. Use larger bottles in older children.

A letter is written on the day of A/R by the doctor who saw the patient (countersigned by one of the consultants). The child's named consultant will write the final report once all the results are collated. When the child is reviewed by the consultant in the next clinic, a letter is sent in the usual way, highlighting the discussion over any changes made as a result of the annual review. All data is entered on to our own hospital database and the UK CF database (PortCF), for which the parents will have given written informed consent.

PortCF

Annual review information is entered on to the CF Trust national database – PortCF which is mandatory. Website – www.portcf.org.uk. User name to access our data can be obtained from Jackie Francis.

3.3 Transition Clinic

Transition 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 of Adult CF Centres and provide information about growing up with CF. The Adult CF Clinic at the Brompton Hospital may not be the Centre of choice for some patients – advice is given on how to access other services with contact details for each centre. Either way we will make the necessary referrals.

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 we plan to transition of all young adults by their 17th birthday. A transition document detailing family, social and clinical history is completed by each patient, their family and clinical nurse specialist and given to the adult team in preparation for their transition clinic (see Appendix I). There is an optional section entitled ‘all about me’ which can be filled in by the teenager.

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 Di Bilton or Dr Nick Simmonds.

The children 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.

3.4 Homecare Service (nursing & physiotherapy)

The role of the Homecare Service is to provide a specialist nursing/physiotherapy input at home, and to facilitate the continuity of care between the Royal Brompton Hospital, local services and the family. The team currently consists of three trained children’s nurses both with children’s community nursing experience; and two physiotherapists (who job share) specialising in providing homecare for children with CF and their families. Criteria for referral are that the child attends RBH as their specialist centre and lives within the M25 (although at the Homecare team’s discretion it is sometimes possible to visit outside of this boundary).

The Nursing service operates Monday to Friday 9am to 5 pm.
The Physiotherapy service operates Monday, Tuesday, Thursday and Friday 9am to 5pm.

Contact for families and professionals are via mobile telephone (with answerphone):

07973 173 969	**Pat Stringer** (Nurse Specialist)
07971 224 068	**Katie Dick / Karen Henney** (Nurse Specialist)
07970 269 452	**Emma Dixon** (CF Physiotherapist)
07791 584 749	**Nicky Murray** (CF physiotherapist)

Purpose of visits

- Monitoring and assessment including measurement of SpO_2, lung function and collection of specimen e.g. sputum, cough swabs
  - between routine appointments
  - following a course of oral antibiotics
  - mid course of IV antibiotics
- Flush portacaths / change portacath needles (nurses only)
- Physiotherapy service offers:
  - assessment and review of airway clearance techniques
  - advice on exercise, posture correction and stress urinary incontinence
  - education on inhaled medication use and regimens
- Education, reinforcement and encouragement following:
  - diagnosis
  - diagnosis of new complication
  - commencement of new treatments
- Support.
- New Born Screening
  - The screening labs inform the CF nurses of babies who have been screened "highly likely" to have CF.
  - The homecare nurses with support from local heath visitors, visit the families at home to inform them of the suspected result.
  - The homecare nurses are able to answer parent's questions with specialist, up to date knowledge.
  - Parents are given an appointment for their baby to attend the Royal Brompton Hospital the next day for a sweat test where they will meet with the Consultant and a formal diagnosis made.

Home visits offer families the undivided attention of a health professional away from a busy ward or clinic in the security and privacy of their own home. This provides the opportunity for less hurried discussions about anything the family wish to talk about. In particular, practical issues can be dealt with and it gives us an opportunity to explore how the family is coping with the situation of living with a child with CF. Home visits can be an ideal opportunity to involve both parents, the child, siblings and extended family members. In order to maximise the effectiveness of visits, appointments are made with the family responding to their individual needs regarding frequency and content. The team will endeavour to make appointments at a time convenient to the family and school aged children can be seen after school. Additional contact, support, and follow up are also maintained by telephone on a two-way basis. Home visits should not be allowed to be a substitute for regular clinic attendance.

Liaison

The team aims to establish links with local services as appropriate to each individual child in order to promote continuity of care. The Homecare service is not a replacement for local services but aims to complement them in providing a specialist resource.

Liaison occurs regularly with:

- Community Children's Nurses
- Health visitors
- School nurses & teachers
- GPs
- Practice Nurses
- Social workers
- Community physiotherapists
- Community dietitians
- Psychology services

The team regularly sets up "shared care" with local Community Children's Nurses and Physiotherapists, visiting alternately (or as required) and on occasions jointly, ensuring telephone communication following visits and outpatients appointments. The team offers GPs a visit when children are newly diagnosed or new to their Practice. They liaise regularly regarding medication requirements, linking also with local pharmacists. The team visits schools at parents'/carers' request to educate school staff regarding CF and the particular needs relating to the child during their school day. The homecare team will train teachers for school residential trips to ensure the child can attend without missing vital treatments. If requested by the child, class talks can be given allowing greater understanding of CF by their peers.

Liaison with the multi-disciplinary team at the RBH –

- Team has direct access to medical advice at RBH at all times, and will consult with medical staff from the home as appropriate.
- All team members attend a weekly multidisciplinary team feedback meeting at RBH where every patient seen the previous week is discussed.
- The community nurses cover the CF outpatients' clinic when the in house Clinical Nurse Specialist is away. The respiratory ward round is also attended by one of the team. The team works closely with the Hospital CF nurse specialist.

3.5 Clinical Psychology

The clinical psychologists can meet with parents, children with CF, their siblings, family, friends and other carers. They provide a service to both inpatients and outpatients. They are available during CF clinics and Monday-Friday during working hours. They also offer a consultation service to other members of the CF team and are happy to discuss case management or referrals. The clinical psychologists attend ward rounds and weekly multidisciplinary CF clinic meetings.

The clinical psychologists recognise that CF can affect a child and/or family in a variety of ways. We offer the opportunity to discuss any fears, anxieties or problems that can arise when a child and family are living with CF. As well as talking and listening, clinical psychologists can offer suggestions for change and practical ways of coping with difficult situations such as managing blood tests. Any assessments and interventions carried out will be made sensitive to the needs of the child and/or family and may include working confidentially if required. The permission from parents will always be sought prior to a clinical psychologist formally introducing her/himself to a child. Sometimes the psychologists will liaise with local services as long term follow up is often better carried out locally nearer to the family's home. This is always agreed with the family first.

Some 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 child cooperate with medical treatments e.g. introducing nebulised medication
- Checking and informing (often with a medical or nursing colleague) the understanding of the child has of their illness, and consideration of future treatments that may be offered along with the implications e.g. home oxygen
- Managing invasive procedures including fear of needles
- Feeding behaviour
- School problems
- Mood problems
- Changes in behaviour/personality which may or may not be associated with the CF
- Considering transplantation
- Issues towards the end of life

The department has a number of information leaflets which are available on the intranet:
- Paediatric Clinical Psychology Service
- Help with having blood taken
- Teaching you child to swallow enzyme capsules whole
- Introducing your child to nebulisers

3.6 Social work support

The Paediatric Social Worker is a member of the multidisciplinary team and will accept referrals and self-referrals to work with children and families.

The remit of the Social Services Department is defined by legislation. Relevant to children are the Children Acts of 1989 & 2004. The social worker's role is primarily to undertake an assessment of the child and families need for support throughout treatment and on discharge from hospital.

Such work includes:

- Primarily working with children and their families who are in-patients at the Royal Brompton Hospital.

- The Paediatric social worker will meet with the family and liaise with the necessary health professionals and undertake an initial needs assessment. This will involve gathering

information from the family and also the appropriate medical/nursing staff and often the Home Local Authority. Since most patients are not resident within the Royal Borough of Kensington and Chelsea the Paediatric social worker having completed an initial assessment will refer on to the patients' local authority social services department.

- Assessing and identifying with families their strengths and resources and any perceived needs for practical, social, emotional and psychological support that they consider will enable them to function at their best.

- Eligibility criteria and the availability of resources vary in different local authorities. The responsibility to provide services lies with the home local authority and they will wish to undertake their own needs assessment when the child is discharged from hospital.

- Exploring and identifying ways and means of meeting those needs which often involves giving information about statutory and voluntary frameworks and available services.

- The Paediatric Social Worker works closely with the Welfare Rights Advisor at the Brompton Hospital. Advice can be sought on applications for DLA and specialised charities, in connection with a child's condition and the care she or he needs. See appendix IV for details of benefits available in relation to the daily attention & supervision required by children with cystic fibrosis from their parents/carers.

3.7 Family Liaison Team

They support parents and carers during their child's hospital stay, particularly in relation to non-medical issues. They are able to help families if problems arise either in hospital or at home. They can also liaise with others members of the multi-disciplinary team on behalf of the families. Being far from home can be stressful, particularly if other children and partners are still at home, and our aim is to try to alleviate that stress.

4. Admission to hospital

There are several reasons why a child with cystic fibrosis is admitted to hospital, which include the following:

- Education of family at time of new diagnosis.
- Bronchoscopy & pH study for newly diagnosed patients.
- Any deterioration in clinical condition that fails to respond to out-patient measures e.g. chest exacerbation, DIOS, CFRD.
- Elective 3 monthly admissions for IV antibiotics (usually 2 weeks).
- Elective 1 monthly admission for IV immunoglobulin (usually overnight).
- Elective operations e.g. portacath or gastrostomy insertion, ENT or dental operation.

4.1 Admitting the child

Pre-admission

If an admission date is certain (unlikely to be until day before) then it may be possible to pre-order the IV antibiotics using the CIVAS (Centralised Intravenous Additives Service); this is especially useful if the admission is on a weekend.

History & examination -

On admission, the reason for hospital attendance must be identified, and documented clearly in the integrated care pathway (currently used for IV antibiotic admissions), which is available on the intranet and on Rose ward). Clerking should be followed in the integrated care pathway with emphasis on the following-

- Respiratory system: - cough, wheeze, sputum production (quantity, frequency, colour, consistency), haemoptysis, chest pain/tightness, dyspnoea, exercise tolerance.
- Gastrointestinal system: - appetite, heartburn, water brash, funny taste in mouth, nausea, vomiting, frequency bowels are opened, quality of stool, abdominal pain, rectal bleeding, weight loss, calorie supplements, gastrostomy/NG tube feeds (amount, type, nights per week).
- Genito-urinary system: - thirst, urinary frequency, polyuria, nocturia.
- ENT: - nasal obstruction, epistaxis, rhinitis, sense of smell & taste.
- Neuromuscular - headache, paraesthesia, muscle weakness, joint pains, backache.
- Pain.

The most recent positive sputum culture result should be documented with full sensitivities. Certain bacteria like *B cepacia* complex and MRSA require specific action with regards to therapy and isolation from other CF patients.

The most recent & patient's best (within the last year) pulmonary function tests (FEV_1, FVC) must be recorded. A trend plot of previous lung function may be available for the respiratory technicians.

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 or their parents before recording and prescribing them. This must include doses of inhaled medication – write inhaled steroids in mcg **not** number of puffs. If a patient is on oral steroids, record the starting date and dose/kg/day. 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). Check it is also written on the front cover of the notes. Nebulised antibiotics are always continued when a child is receiving intravenous antibiotics, but we use an alternative drug, ie, if they are on IV tobramycin they receive nebulised colistin, and if on IV colistin they receive nebulised tobramycin.

Drug histories are confirmed by a pharmacist at the earliest opportunity within pharmacy opening hours.

A full social history should be taken paying particular attention to school attendance, housing, pets and active/passive smoking.

Examination

Examination findings should be recorded in the standard way according to systems. Do not forget the ENT system, particularly nasal polyps. Blood pressure is mandatory on all patients, with particular attention paid to those on oral steroids. Check presence of glycosuria on all patients.

All children should have the following observations recorded:

- Weight (kg & centiles) in vest/bra and pants only. If the child has been weighed fully clothed they must be weighed again. Obtain photocopy of patient's CF growth chart from the CF secretary / CF nurses.
- Height (cms & centiles).
- Head circumference in <1 year olds.
- Temperature.
- Oxygen saturation in air or oxygen (include O_2 requirement).

4.2 Investigations

All children old enough will have **pulmonary function tests** (spirometry) performed following admission. If the child has been admitted from clinic, these will already have been performed and do not need repeating**. This must be performed within 24 hours of admission.**

All children require **admission bloods**. These are generally performed at the same time as the first aminoglycoside level unless they are needed immediately – this is to minimise exposure to needles. For blood sampling, try to use veins on the back of the hand so that their

antecubital fossae veins can be reserved for long lines. For all infants and children we use anaesthetic cream (EMLA) applied under an occlusive dressing for 60 minutes. Avoid Ametop due to the high frequency of allergic reactions, especially in atopic children (it may be tried if there has been a previous reaction to EMLA). You can also use Cryogesic® spray (ethyl chloride) which can be used immediately before the procedure, but it won't last longer than 2 minutes so is only suitable for very short procedures**.** If coping with needles has been difficult in the past, please discuss this with a play therapist or a clinical psychologist in advance for help and support, and if necessary, defer testing unless it is absolutely urgent.

The list of blood tests (with the appropriate bottles) required on admission is given below:

• **Full blood count (FBC)**	**EDTA (pink) 1ml**	**Haematology**
• **Urea & electrolytes**	**serum (brown)**	
• **Liver function tests**	**serum (brown)**	
• **Calcium, magnesium, phosphate**	**serum (brown)**	**Biochemistry**
• **Glucose**	**serum (brown)**	**3 ml minimum**
• **HbA_{1c}**	**serum (brown)**	
• **Total IgE**	**serum (brown)**	**(alternatively**
• **Aspergillus RAST**	**serum (brown)**	**lab will accept**
• **CRP**	**serum (brown)**	**clotted blood)**
• **Aspergillus IgG**	**serum (brown) 1ml**	**Virology/Immunology**

If the child is due annual review (usually around the time of their birthday) within next 3 months, make sure all annual review bloods are taken (usually just add IgG, serum vitamins, clotting) on day 2 when aminoglycoside levels are taken - see list on section 3.2. Remember to also complete the annual assessment paperwork, chest x-ray and arrange formal lung function for the end of the admission, usually on day 9-10.

A **chest x-ray** is only performed if clinically indicated e.g. to exclude pneumothorax or for annual assessment. They are **not** performed to check long line position.

Sputum/cough swab must be sent to microbiology within 24 hours of admission. **Nasopharyngeal aspirate** for viral immunofluorescence is sometimes indicated (usually under 1 year old).

Urinalysis must be performed on admission especially if the child is on oral steroids or there is a recent history of weight loss

Further investigations during admission:

- Twice weekly weight (Tues, Fri).
- Twice weekly spirometry (Tues, Fri).
- Daily BP and urinalysis if on oral steroids.
- Aminoglycoside levels 23 hours after 1st dose (i.e. before 2nd dose), and if in desired range, repeat 1 week later. **Record results on drug chart.**
- Once weekly U + Es if on IV colomycin.

- 3-weekly WBC if on chloramphenicol, so not routinely required unless having >2weeks course
- Weekly FBC if on linezolid
- Monthly LFTs + FBC if on voriconazole
- Monthly LFTs if on itraconazole
- Weekly sputum / cough swab.
- Overnight SpO_2 (Nelcor) early in admission, especially if FEV_1<50% or resting SpO_2 <92% (see section 6.12).
- Daily SpO_2 unless initial one >95%.

4.3 Venous access & long line insertion

All children will require venous access for administration of IV antibiotics. If they have a portacath in-situ, the nursing staff will generally insert the gripper needle. Otherwise long lines are our preferred method of access; however there are occasions when a short cannula or central venous access will be necessary. Long lines are usually inserted by the SpR but may be inserted by the SHO once they have been signed up as having achieved competency under the supervision of an SpR (see SHO long-line assessment form – appendix VI).

Some children will require sedation prior to long line insertion. In suitable children, Entonox (nitrous oxide) should be the first choice. There is a separate guideline for its use available on our intranet. If oral sedation is required, it can be achieved after 30 minutes following administration of oral midazolam (0.5mg/kg, max 15mg) or after 15 minutes following sublingual midazolam (<10 yrs - 0.2 to 0.3 mg/kg, max 5 mg; 10 yrs or over is 6-7 mg dose). In accordance with the trust's sedation policy, all children having sedation (including Entonox) must be kept nil by mouth for 6 hours (clear fluids up to 2 hours) and written consent for sedation is required. After vein selection, local topical anaesthesia should be offered (EMLA).

We currently use Vygon PICC lines which are 30 cms in length. Measure the distance externally from the vein to where you wish the tip to lie (the medial end of the clavicle is the usual position for lines inserted in the antecubital fossa). We do not routinely x-ray these lines but should the child have an x-ray for another reason don't forget to check the position of the line.

The equipment required is:
- long line (Vygon). Each pack contains: catheter x 1, splitting needle introducer x 1, 10 ml syringe x1, fenestrated drape x 1
- surgical gown
- sterile gloves
- chlorhexidine swab stick x 2
- non-toothed forceps
- sterile scissors
- 1 x pack
- steristrips
- clear sterile dressing (IV 10000)
- 10ml 0.9% saline
- 10mls heparin saline

- 10ml syringe x 1
- green needle
- bionector
- bandage

Position the patient in a comfortable position with the arm extended. Remove the anaesthetic cream and use a tourniquet. Wash hands and put on sterile gloves and gown. Flush the catheter with 0.9% saline to ensure that line is intact. This is a sterile technique so clean the skin with a chlorhexidine swab stick and then place a sterile drape around the arm/leg to create a sterile field. Veins in the antecubital fossa are the preferred sites of insertion (preferably the side the child does not use for writing). An assistant should tighten the tourniquet.

Cannulate the vein and observe for a backflow of blood. Hold the needle stationary and advance the sheath. Release the tourniquet and remove the needle. Thread the line using sterile toothless plastic forceps. If obstruction is encountered try: a) stroking the arm along the line of the vein, b) moving the arm from the shoulder, c) flushing whilst advancing the line. If any sign of swelling or pain occurs then stop. Once inserted to the desired length, flush with sterile heparin saline to confirm patency. Split the introducer sheath and apply gentle pressure to the exit site to stop bleeding. Cut a small piece of gauze on which to place the bevel of the long line prior to securing with a sterile clear dressing. Connect the bionector and cover with a bandage.

Thrombophlebitis - there is some anecdotal evidence for the use of hydrocortisone in long lines complicated by thrombophlebitis. It is **NOT** suitable for blocked lines. It appears to be safe and can be repeated as necessary. The steroid dose is minimal so there should not be any steroid adverse effects. If it is going to work it will usually do so after 24 hours

1. Give IV antibiotics in the usual way.
2. Use 3 mg hydrocortisone made up to 3 mls (with 0.9% normal saline) into PICC line.
3. Leave in line until next dose of IV antibiotic.
4. Aspirate and flush line in the usual way prior to IV antibiotic.
5. Concurrently use 0.5% or 1 % hydrocortisone cream topically on arm (over erythematous area).

Taking bloods from portacaths has been associated with an increased risk of thrombosis, so generally we would try to avoid doing so. However this must be carefully weighed against the potential benefits, particularly for needle phobic/aversive children. Regardless of this, blood aminoglycoside levels must NEVER be taken from portacaths or longlines.

Consider use of urokinase if long line or portacath are blocked.

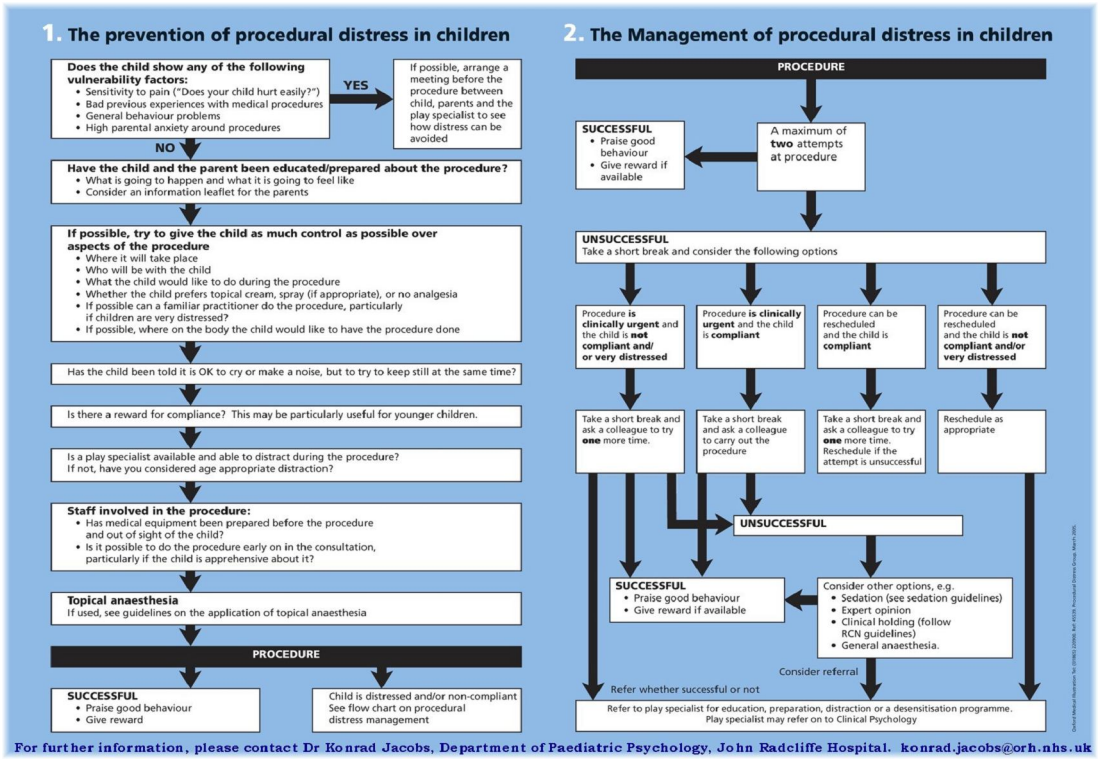
4.4 Procedural distress

Preparation and planning with the child and family is essential to help them to cope. Try to ensure that the play specialists are involved and when necessary, the clinical psychologists. The following are some suggestions for managing an invasive procedure when you know that the child or adolescent is very anxious:

- Ask what has helped previously if/when the child had a good experience

- Give the child some choice e.g. which arm, who they want in the room, what they want to talk about, what distraction has worked in the past etc. Talk to the parent/carer accompanying them about their role ie, who they want to come in to the room, who will hold the child, positioning the child, soothing the child and above all modelling calm themselves. Make an agreement with the child about how many attempts you will have and do not exceed it. This may mean that you have to take a break and try again later. Do not be afraid to ask someone else if you have missed twice.
- Consider the timing of procedures, as far as possible keep to the agreed time and do not leave the child waiting beyond this.
- Make sure all equipment is ready before you get the child into the treatment room.
- At annual assessment try to do bloods at the time that the child/family have indicated would be best for them. Many children prefer to get the blood test done first, EMLA cream can be sent home for parents to apply before arriving at clinic.
- Consider who should carry out the procedure. If a child is already known to be highly distressed they would benefit from an experienced and confident clinician undertaking the procedure. They must never have the procedure attempted by an inexperienced clinician.
- Discuss what reward the child will receive once the procedure is completed.
- Focus on (even small) signs of coping by the child
- Try to set a time limit, a distressed child is unlikely to change their mind and agree to a procedure that they have been refusing for half an hour. Take a break, re-plan and try again if necessary.
- The use of sedation, and at times restraint, should be discussed at the planning stage and not used 'in desperation' when a procedure has been unsuccessful.

Managing invasive procedures - In order to minimise the likelihood of inducing procedural distress, please follow the flow chart below when undertaking any invasive procedure with a child or adolescent. Guidelines from Oxford Radcliffe Hospitals Multidisciplinary Procedural Distress Group, 2005.



4.5 Discharge

All children should have a discharge letter done on Infoflex before discharge. There is a specific CF summary, which includes:

- General conclusions about the admission
- Weight on admission & discharge
- Spirometry results (FEV_1, FVC) on admission & discharge
- All drugs on discharge (including any weaning) - This will be linked with the computerised pharmacy discharge system (JAC).
- Plan for review - when / where
- Relevant results including positive microbiology
- Pending results
- Plan for tests necessary at home (e.g. WBC after 3 weeks if still on chloramphenicol)
- Date of next admission if elective (3 monthly IVABs, monthly IV immunoglobulin)

A copy of the discharge should be given to the parents and it should be emailed to the CF secretary for co-signing by consultants and distribution.

The summary must put the following as primary reason for admission:
'Planned management of cystic fibrosis disease'.

4.6 Infection control

There are concerns about cross-infection between children with CF and these dictate that certain precautions need to be adhered to for all CF children. Since 2006, segregation has been in place in clinic and for in-patients, including in the school rooms etc to minimise contact between CF patients. There is an undoubted downside in that social interaction is severely curtailed, and we believe the children benefit from talking to each other so do not wish them to be in 'solitary confinement'. However many families are anxious about cross-infection and this view must be respected. Although our ward staff will support and reinforce these measures, we will have to rely on the parents/carers helping to ensure the children stick to the rules.

Generally, personal hygiene is emphasised and children are encouraged to put their hands in front of their mouths when coughing, then to wash their hands (front and back, and all spaces between). Hands should be washed regularly and they must be taught not to share (with other CF children) cups, cutlery and so forth.

The formal rules are summarised below:

1. Ward

- Each patient will either be in a cubicle or in a bay with no other CF patient. No other CF patient or parent is permitted to be in that area at any time. **Children with CF should not enter any other CF child's room.**
- We try to separate children with CF and those with non-CF bronchiectasis / PCD although this is not always possible.
- We want to discourage waiting around in corridors on the ward.

- No sitting or waiting around the nurses station, including during the evenings.
- Disinfectant hand rub dispensers are outside each cubicle and each bay for use by staff, all children, families and visitors.
- Doctors must clean stethoscopes between patients.
- We realize that some bathrooms are shared and can do nothing about that. However there will be medicated wipes available for parents to use if they wish, before their child uses the bathroom.
- Physiotherapy is carried out in the children's own rooms only. When coughing up sputum, sputum pots with covers should be used, but if tissues are preferred, these should be disposed of immediately in a yellow bin bag.
- Children infected with MRSA or *Burholderia cepacia* will stay inside their cubicles for the whole admission, although may spend time off the ward. They must not use the cubicles which have shared bathrooms & toilets (Lagoon South).
- Patients with the different organisms in their sputum will not be looked after by the same nurse where possible.

2. Daily Plan

- The daily plan is an integrated plan to be used by the whole multidisciplinary team to timetable in appointments, investigations, treatments and school. This will help the children know what is planned for each day. The plan will be kept by the beds.

3. School Room

- School is compulsory (by law).
- The school has 3 separated areas, primary, secondary and school room/music room.
- There will be one CF child in each area only at any time. CF pupils will have access to the schoolroom according to their daily plan.
- They will also be provided with school work from the teachers that they can continue with by their bed space.
- The relevant area is cleaned between patients.

4. Playroom

- Rules for the playroom are similar to school rules.
- There will be one CF child in the area only at any time. CF children will have access to the playroom according to their daily plan.
- Play sessions will be arranged by the play leaders at the bedside at times when another CF child is having their turn in the playroom.
- The children will not be able to eat in there, but have meals at their bedside. We are arranging to buy tables to go by each bed.
- The relevant area is cleaned between patients.
- Playroom staff finish at 5pm and the playroom closes after supper.

5. Youth Club and School Holiday Program

- When these take place in the school room, the same rules apply as with standard school time**.**

6. School trips & other outings

- The school is committed to equal opportunities and all children will have access to school trips and outings during their admission, assuming they are well enough. We will have to manage transportation to ensure our guidelines are adhered to (ie, we do

not want several children with CF in one minibus). However more than one child with CF may be at the venue e.g. park, museum etc. at the same time. If parents do not want them to go, this will be respected but parents must enforce this.

Specific organisms

Particular care is necessary for children who are infected with -
- *Burkholderia cepacia* complex
- MRSA
- Multi-resistant *Pseudomonas aeruginosa*
- Respiratory viruses e.g. RSV or Influenza

The following organisms are not of particular concern –
- *Stenotrophomonas maltophilia*
- Non-tuberculous mycobacteria (NTM)

The risk of transmission is related to the level of intimacy of contact. The child is put into a room with private washing and toilet facilities. Items including toys and TVs should be kept in the room and washed when taken out, before use by another child (this includes a stethoscope). Hands are washed and rubbed with Hydrex before entering and leaving the room. Socialising with other children is discouraged and visiting other children in their rooms or being visited by other patients is not allowed. It is important not to stigmatise patients and the reasons for their relative isolation must be carefully explained. It is also important that children with *B cepacia* realise that they do not pose an infection risk for healthy school friends. Relatives of patients colonised with MRSA may also carry the organism. Nasal swabs will confirm this.

Bactroban (mupirocin) nasal ointment may eliminate the organism but recolonisation frequently occurs. Staff who have nursed such patients should also be screened (check with Infection Control Team). Children with *B cepacia* do not attend the CF clinics but come to general respiratory clinics and they do not mix with other CF children in the hospital school & playroom. Those with MRSA come to the 2nd Friday of the month MRSA CF clinics when no other patients are seen. Patients with *S maltophilia* are no longer put in the same category as regards isolation as those with MRSA or *B cepacia,* as our experience and a number of publications have shown the organism is not a major problem in CF.

Segregation clinics

Introduced in January 2006, and it is difficult to assess the benefits in terms of cross infection, and potential disadvantages (social isolation and loss of the mutual support that the families and children can offer each other).

- Clinic appointment letters give a specific appointment time and this is now crucial. It is very important that these times are kept to, so that the clinics run smoothly. If patients arrive early, we will have to ask them to leave the clinic area until the allotted time unless a clinic room happens to be available. We will then contact them on a mobile phone if the room becomes free early. If they are late for the appointment, they may have to wait until the end of clinic to be seen. These clinics are very complicated to run hence the need for such a rigid policy.

- Each child is allocated to one room, and all the members of the CF team (physiotherapist, dietitian, doctor, CF nurse) come to see him/her in that room. The clinical psychologist will see the children elsewhere due to time constraints.

- All procedures are undertaken there (height & weight measurement, lung function, cough swab/sputum collection, blood testing).

- There will be no sitting in the waiting area as children will only be in their own clinic room; we will encourage children to bring their own toys and books etc with them. At the end the family leaves out-patients immediately.

- Between patients, the room is thoroughly cleaned (desktops, chairs, other surfaces, sinks) and the next patient enters.

- We will continue to have free slots at the end of clinics to see children at short notice who have become unwell and phoned us urgently. Patients must not arrive without telephoning to book a slot however. Of course, all children needing to be seen will be seen, as is now the case.

- It is important appointments are cancelled if the child is not coming, in order not to waste a slot.

- Annual reviews will continue to take place in the clinics. We hope to organize it so that most of the tests that take place out of the clinic (ventilation scans, formal lung function, x-rays) are carried out in the morning before clinic starts, there will be time for lunch and they will be seen in the earliest slots.

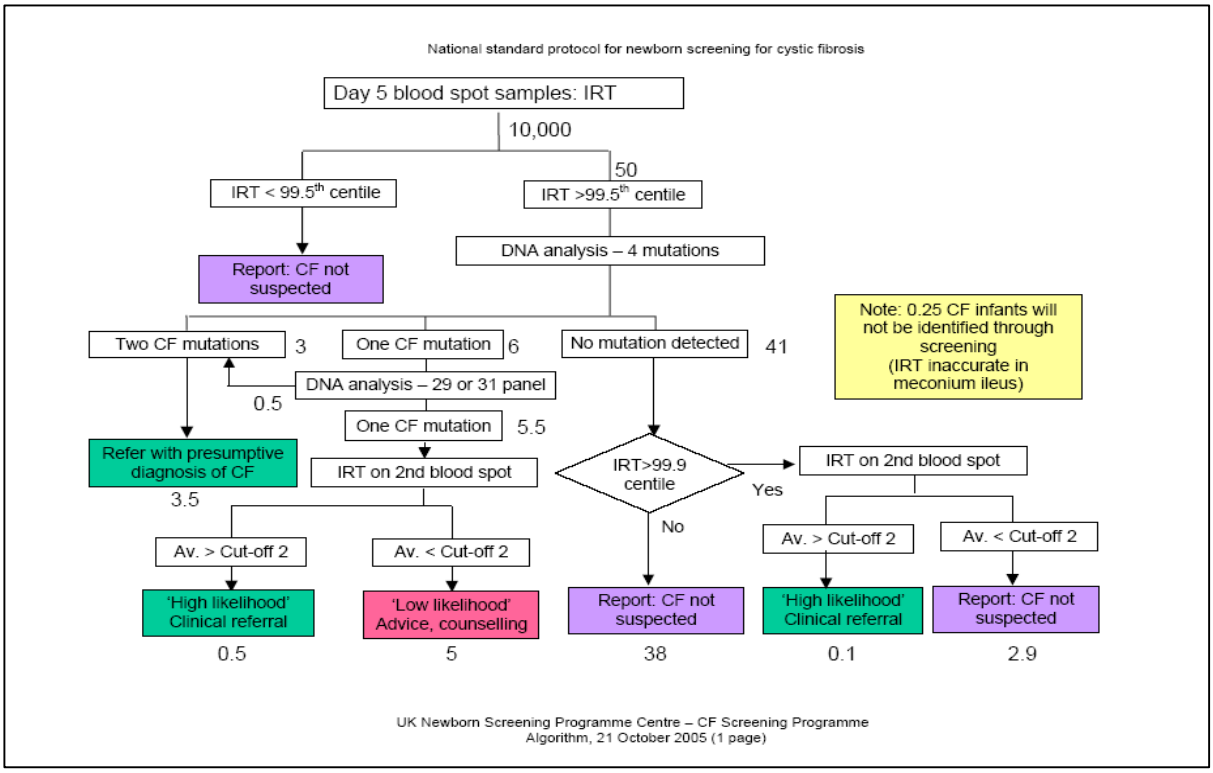
5. Making the diagnosis

Since 2007, newborn screening for CF has been in place throughout the whole of the UK. At our centre, the majority of new diagnoses have been through this route, or have been made in an older sibling of a screened baby. Conventional methods of diagnosis are still used to confirm the screening results and will be needed for the small proportion of CF children (estimated at 3 per year for Pan-Thames region) in whom the diagnosis was missed by screening. These will often have a mild phenotype (atypical CF).

5.1 Newborn Screening

Immunoreactive trypsinogen (IRT) is measured on a dried blood spot obtained on the Guthrie card at day 6 of life. Samples with abnormally raised IRT levels will undergo CFTR mutation screening as per the flow chart (see below). Some children require a second heel prick. Positive screen results are conveyed directly by the screening laboratory to the centre. Our practice is then to arrange a visit to the family with the local Health Visitor. Here it is explained that CF is likely and that a visit to the Royal Brompton for confirmation of the diagnosis has been arranged for the following day. A sweat test (see below) is performed, which is mandatory, to rule out any possibility, that screening samples have been misidentified. Results are available within an hour, allowing the diagnosis to be confirmed to the family by one of the Consultant team, who will have first met them when the sweat test is being set up. The basics of CF may be discussed but at this time of great stress, we attempt to limit the amount of information conveyed to parents, most of which will be discussed at the Education Admission. Similarly, screened babies are usually well. Treatment will usually not be initiated at this time with the exception of pancreatic enzyme supplements if symptoms are suggestive of pancreatic insufficiency.

The Education admission will usually occur sometime in the next week. Families are admitted to the ward for a 2 day period, although if local enough, they may return home overnight. A schedule is pre-arranged to ensure that time is spent with each member of the MDT.



Older siblings of babies diagnosed by screening will have a sweat test; usually the parents are keen for this to be done soon as they have an extra thing to worry about. However it is not advisable to do this during the education visit as we have had a case of an asymptomatic older sibling being diagnosed at that difficult time; offer to do this before the visit so the parents have one less thing to worry about, or arrange for the local hospital to do it.

5.2 Clinical presentation

This will become rarer and rarer with time now newborn screening is underway. It is essential that the diagnosis is not ignored or 'ruled out' if a baby has been born since screening began as screen failures do occur. Additionally, children born before screening may present late with clinical features, as will babies born abroad. Lack of experience of clinical staff may actually lead to further delays in diagnosis in such groups of children. The history and/or examination will usually raise suspicions of the CF diagnosis. Common features are recurrent respiratory infections and failure to thrive with steatorrhoea (but do not be fooled by the thriving child). Other features in a baby that mean CF must be excluded include meconium ileus, rectal prolapse, salty tasting skin, prolonged obstructive jaundice, and unexplained haemolytic anaemia, hypoalbuminaemia and oedema. Finger clubbing and nasal polyps in an older child are also important, as is isolation of *S. aureus* or *P. aeruginosa* from the respiratory tract. Confirmatory investigations are outlined below. If in any doubt, we do a sweat test, and if anyone at all (including parents) is worried about CF, we do a sweat test.

5.3 Sweat testing

Sweat testing will reliably make the diagnosis in 98% of patients. Despite the availability of genotyping (and because of its limitations) the majority of children in whom CF needs to be excluded will undergo sweat testing. This group will include the following:

- child with suggestive history / symptoms/ examination.
- sibling of a known case (even if asymptomatic).
- more distant relative of known case if clinical suspicion.

We perform the sweat test using the macroduct system, as opposed to the older 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. Sweat testing can be performed once a baby is > 48 hours old although often inadequate samples are obtained in the first few weeks.

As with any of these techniques, it is extremely important that they are performed by personnel who are experienced. Only the CF nurse specialist, Day-case nurse or trained out-patients nurses 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	Cl^- <40 mmol/l; but <30 mmol/l in newborn screened babies.
Needs repeating	Cl^- 40 or 30 (latter in newborn) up to 60 mmol/l (although in infants, this is still highly likely to be CF).
CF confirmed	Cl^- >60 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 4 standard deviations above the mean (Farrell PM et al. Pediatrics. 1996;97:524–8). There is currently discussion within the UK, which is likely to lead to these values being adopted; we consider it sensible to be cautious about ruling out the diagnosis in a child with a high index of suspicion and an intermediate sweat electrolyte value. 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 2 sweat test results not one, we take 2 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 increasingly 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 would be the appropriate next step (see below). Discuss nasal potential difference testing with Dr Jane Davies (see later).

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.

Fludrocortisone suppression test. In grey cases with repeat levels in the intermediate range, this test may help differentiate CF from normal. We do not perform this now as we have access to nasal potential difference testing and extended genotyping is more available. Oral 9α-fludrocortisone is administered at a dose of 3 mg/m^2 (see tables for body surface area – appendix V) 48 and 24 hours before a repeat sweat test. In normal subjects, the sweat electrolyte values will fall, but this does not happen if the patient has CF. In the BNF, the only dose of fludrocortisone tablets available are 100 mcg. However the Brompton pharmacy can provide 1 mg capsules for this purpose (round dose up or down for convenience). Consultant decision to perform this – note original paper was in adults, there are no paediatric data.

5.4 Genetic analysis

There are currently at least 1500 mutations in the *CFTR* gene which have been reported to be associated with the clinical picture of CF. Mutations fall into different classes (I-V), with commonest in the Caucasian population being a class II mutation, ΔF508. Nomenclature has changed recently (see appendix XI).

Indications for genotyping include the following:

- Any child diagnosed with CF:

  - facilitates screening for other family members.
  - allows prenatal diagnosis of future pregnancies.
  - With the advent of mutation-specific therapies, all CF patients should be genotyped to allow inclusion into clinical trials and, in possibly to direct future treatment
- In newborn siblings of affected children, cord blood should be taken at the time of birth (arrange with mother in clinic, give form and blood bottle).
- Generally older siblings will have a sweat test rather than genetic analysis.
- To aid confirmation of diagnosis in case of borderline sweat test.
- Note that carrier testing is **not** carried out in siblings until they are old enough to decide whether they wish it done (mid teens).

Based on current knowledge, genotype analysis should not be used to guide prognosis in an individual child, 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

Due to the large number of identified mutations, and the extreme rarity of many of these, it is only practical to screen for a few on a routine basis. This will usually includes the commonest 5, 12 or 31 mutations Therefore failure to detect mutations does not exclude the diagnosis. The above is of particular importance in a child of non-Caucasian origin. There is now a specific panel of mutations, which are common in the Asian community. It is therefore CRITICALLY IMPORTANT that in every case the child's ethnic origin is included on the request form so that the most likely mutations can be looked for. Extended screens can be performed if specifically requested but are expensive (in the order of £300) and time-consuming and therefore not done routinely, for example in the case of a clear-cut biochemical diagnosis. Samples should be sent to the Kennedy Galton Centre (KGC, see below). Samples for extended analysis should be specifically marked as such, and will be sent by KGC to Manchester.

Antenatal screening

Carrier parents contemplating another pregnancy should be referred for genetic counselling in order to 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 fetus.

On the basis of the limited number of mutations screened for, some CF children will be, for example, ΔF508/-, 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.

When the mother of a child with CF has a subsequent pregnancy, it is important that when they are in clinic with their CF child, we discuss the possible outcomes of the pregnancy. Specifically, the baby is at risk of meconium ileus (particularly if we know the first child is ΔF508/ΔF508 should it turn out to have CF. Our advice is that the child is not taken home until it has established feeding and had a normal bowel motion. In addition, we recommend that a cord blood sample is taken for DNA analysis, and we give the mothers a form for CF genetics with the relevant blood bottle (EDTA red bottle) to hand to their midwife. The cord blood result is usually ready before the Guthrie card CF screening result is available. We expect that the mother will have informed their obstetrician that they already have a child with CF.

Pre-implantation diagnosis

For parents wishing to consider pre-implantation diagnosis, to ensure an unaffected fetus, 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 -

Alison Lashwood
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

Practicalities of genetic testing

Take blood (2-5ml) into EDTA bottle.
Complete genetics form.
Samples need to be either given to Jackie Francis or sent to our Clinical Biochemistry Laboratory who will forward them.

Samples from outside the Royal Brompton Hospital should be sent to:

DNA Laboratory (Cystic Fibrosis)
Kennedy Galton Centre
Level 8V
Northwick Park & St Mark's NHS Trust
Watford Road, Harrow
Middlesex HA1 3UJ

Tel: 0208 869 3180

Extended genotype testing is conducted by –

Regional Molecular Genetics Service
Genetic Medicine
6th Floor
St Mary's Hospital
Oxford Road
Manchester
M13 9WL

Tel: 0161 276 6122
Fax: 0161 276 6606

5.5 Other tests

These may be supportive of the diagnosis:

- **Stool elastase**: low in CF with pancreatic insufficiency (usually <15 mcg/g). Normal levels (are expected by day 3 in term infants and by 2 weeks of age in those born less than 28 weeks gestation, so tests should not be performed before this time.

Normal	> 200	mcg/g stool
Mild/moderate pancreatic insufficiency	100-200	mcg/g stool
Severe pancreatic insufficiency	< 100	mcg/g stool

- **Nasal potential difference (PD)**: difficult in small children as requires co-operation, but may be useful in older indeterminate cases (over 8-10 years). Can be done easily on young children whilst under general anaesthetic, e.g. for bronchoscopy. We rarely obtain useful readings in the presence of nasal polyps or if there has been previous nasal surgery, and it should definitely be postponed if the child has had a cold within the last 2 weeks. It is a difficult and time-consuming investigation and will therefore usually only be done once all other CF investigations are complete. Please refer to Dr Jane Davies (via PA, Gina Leo, g.leo@imperial.ac.uk, 0207 351 8333), who runs a specialised nasal PD clinic monthly. In the very young infant, the limited evidence available suggests that this test is less useful than in older children and adults.

5.6 Routine in-patient investigations for newly diagnosed patients

Based on recent BAL studies showing significant infection and inflammation with impaired lung function in babies as young as several months, even in the absence of symptoms, we investigate newly diagnosed patients (including newborn screened) thoroughly, usually at 6-12 weeks after the diagnosis. In the majority of cases this will include the following:

1. Bronchoscopy with bronchoalveolar lavage and airway wall biopsy

Protocol:

- Macroscopic appearance of airway involvement will be documented as an indicator of severity.

- BAL: 3 aliquots of 1 ml/kg sterile saline instilled into RML or focal area of disease. BAL fractions to be pooled and sent for: MC&S, fungi, respiratory viruses, cytology and fat-laden macrophage count.
- Biopsies +/- airway brushings may be taken, if parents agree, for research purposes. At least 2 good-sized biopsies will be obtained from one side only, and placed in formalin and sent for histology.

Purpose:

- Detection of occult infection. On analysis of the first few years' patients, several new infections (*P. aeruginosa* & *S. aureus*) have been diagnosed.
- Documentation of inflammation based on differential white cell count and histological changes in biopsy.
- Consideration of gastro-oesophageal reflux and aspiration based on staining for fat-laden macrophages.

Research:

Please discuss all children with CF (newly-diagnosed or not) undergoing bronchoscopy or any procedure requiring general anaesthetic *as soon as possible after the decision has been made* with either:

Jane Davies, Consultant, ext 8398, 8333 or mobile via switchboard,
Andy Bush, Consultant, ext 8232 or bleep 1214 or mobile via switchboard,
or the current CF Clinical Fellow.

2. Overnight pH probe to exclude significant GOR

Will be placed whilst under GA for bronchoscopy. Generally, H_2-blockers and proton-pump inhibitors must be stopped 72 hours prior to admission.
3. Consider whether overnight O_2/ CO_2 monitoring might be needed.
4. Ensure that blood has been sent for CF genotyping.
5. Ensure that cough swab sent on admission (useful comparator for BAL culture)

Exclusions to above protocol

- Late diagnosed children with positive sputum cultures in whom little further clinical information is to be gained may not warrant a bronchoscopy.
- Any child who has undergone similar investigations in recent past e.g. as work-up for recurrent chest infections.
- Being extremely well/ asymptomatic is **not** an exclusion criterion.

6. Respiratory care

6.1 Chest exacerbations

If the family is worried they will usually phone the CF nurse specialist or the ward. Sometimes telephone advice can be given (by nurse specialist, SpR or more senior doctor only) but often the patient will need to be seen. Preferred option is in the next clinic, but they may be seen on the ward in special circumstances. Remember with the segregated clinic system the family cannot be told they can turn up any time in the afternoon of the clinic day. They MUST telephone out patients for a time slot. Children infected with *Burkholderia cepacia* complex are seen in non-CF clinics (Tue or Fri am, Wed pm). If the family comes from a long way away, then consider using the local hospital, but brief whoever will see them there and ask for a report back. Some indications of chest exacerbation are:

- Adverse changes in sputum production (volume, colour, consistency).
- Haemoptysis.
- Increased cough, and in particular a new or increased 'wet' cough should always be taken seriously.
- Increased dyspnoea.
- Chest pain or tightness.
- Malaise, fatigue and lethargy.
- Fever > 38º C. Note that most CF chest exacerbations are **not** accompanied by fever.
- Loss of appetite or weight loss.
- Drop in FEV_1 or FVC >10% from previous recording.
- Adverse changes in chest sounds on auscultation (crackles, wheeze). However a clear chest on auscultation does **not** exclude an infective exacerbation. Much more sensitive is palpating the chest while the patient coughs or huffs. New or increased palpable secretions should always be taken seriously.

If the situation is dealt with over the telephone, it is essential that the CF nurse specialist is informed, so appropriate follow up (home care team, telephone) can be arranged. It is important to send (or arrange for GP or local hospital to send) sputum or a cough swab to microbiology; an NPA may be performed in infants. A chest x-ray is only occasionally useful. **A clear-sounding chest does not mean there is no infection present.** Antibiotics should be prescribed, initially orally with IV antibiotics given if the child fails to respond. Do not keep on and on with oral antibiotics if the child has not responded. Whereas it is completely fine to give repeated oral courses to cover viral colds if the child is well between colds, multiple oral courses to the chronically symptomatic, non-responding child are not useful. At most, one general course (e.g. augmentin) and one anti-pseudomonal course (ciprofloxacin, chloramphenicol) should be given before resorting to IV antibiotics. Some children need IV antibiotics from the start.

6.2 Antibiotics

6.2a Policies

- Note that there are many trials being conducted and these policies may need to be modified in light of possible trial entry. *If in doubt, ask.* New born screened babies in the LCCF Early detection of lung disease in newborn screened infants with CF study may need slightly different antibiotics. Please check their notes and see the policy in appendix III.

- **At diagnosis.**
  The question of staphylococcal prophylaxis is based on a few studies only and evidence for benefit is weak. However it is our policy to **use it in all children under 5 years of age**, unless there is a compelling reason not to, *i.e.* not tolerated, or allergy. If the child really will not take flucloxacillin, try another brand if available, or switch to augmentin. In penicillin allergic children, if the history is dubious or uncertain we will test to ensure they have a true penicillin allergy before considering using a macrolide (with a strong history, testing is unnecessary). However, *S aureus* in particular, rapidly becomes macrolide resistant. See formulary section 11.1a for doses.

  Once aged 5 years, flucloxacillin prophylaxis should be reviewed, and only continued if *S aureus* is repeatedly cultured. Oral cephalosporins should not be used for prophylaxis (or if at all possible for treatment) because of evidence implicating this class of antibiotics as causing a greater prevalence of infection with mucoid *P aeruginosa.*

- **Newborn screened child: 1st *Pseudomonas aeruginosa.***
  If grown on cough swab before their initial bronchoscopy, we will go ahead with the bronchoscopy and start them on IV antibiotics putting in a long line under GA to try eradicating it. The LCFC protocol does allow for IV antibiotics for the first Pseudomonas as a clinical decision.

  If the 1st *Pseudomonas aeruginosa* was grown on the BAL only, and not isolated on cough swab done on same day, we will also treat with IV antibiotics. We will then repeat the bronchoscopy at the end of the 3 months nebulisers to see whether the *Pseudomonas* had been eradicated as we will assume we can not rely on a clear cough swab.

- **Indications for long term oral antibiotics.**
  If there are more than 2 isolates of *S aureus* in a year, give prophylaxis with flucloxacillin or augmentin as above (remember under 5s will be on flucloxacillin anyway). If $\geq$ 2 isolates of *H influenzae* in a year, consider augmentin prophylaxis, although evidence is even less secure. Long term azithromycin may be continued for anti-inflammatory/immunomodulatory effects, but it is not good for *S aureus* (due to resistance) and so is not used for prophylaxis. Watch out for *H Influenza* macrolides resistance as well. **Cephalosporins are not to be used** for long term prophylaxis because of worries about increased *Pseudomonas* isolation.

- **Surveillance cultures.**
  Cough swabs/sputum every visit, treatment as below. Culture specifically for non-tuberculous *mycobacteria* on annual assessment visit, in a child who is unwell but culture-negative, on bronchoalveolar lavage, and on admission for an exacerbation. Also when

previously cultured. Remember to write 'CF' as the diagnosis so the laboratory put up the cultures to the panel of antipseudomonal antibiotics.

- **Viral colds at home or in clinic, with no or minor chest symptoms (i.e. not major exacerbation).**
  Always inform the CF nurse specialist or the home care team to arrange at least telephone follow up, and local hospital/GP as appropriate. It is particularly important that this happens for 'out of hours' calls taken by the SpR.

  1. If on augmentin prophylaxis, give treatment dose (i.e. double prophylactic dose for augmentin duo preparation or if using tablets see drug formulary) for four weeks.

  2. If on flucloxacillin prophylaxis - **stop it** (do not double dose as was previous practice). Give treatment dose augmentin for four weeks.

  3. If on no prophylaxis, you must prescribe an antibiotic, which will cover *S aureus* and *H influenzae*. 1st choice is treatment dose augmentin; acceptable alternatives would be a macrolide (clarithromycin or azithromycin). In view of worries over *P aeruginosa*, avoid cephalosporins such as cefaclor unless there is really no alternative. Note that cefixime has no anti-staphylococcal activity, and should not be used in this context.

  4. Oral ciprofloxacin for **2 weeks** if no course within previous 3 months, and previous isolation of *P aeruginosa*. It is a consultant decision to extend course beyond 3 weeks. In general, we try to reserve ciprofloxacin for exacerbations rather than simply to cover a minor cold. The same is true for chloramphenicol which is very expensive in the UK.

- **Positive surveillance cultures.**
  - If the child is well and asymptomatic, a positive routine clinic swab for *S aureus* or *H influenzae* is not necessarily treated, although usually will be. The decision not to treat MUST be discussed with the Consultant. If on flucloxacillin prophylaxis, give double dose *i.e.* treatment dose (50 mg/kg bd) for 1 month.

  - A new isolate of *P aeruginosa* in a child not on treatment for this organism is **always** treated. If the child is known to be chronically infected (& on nebulised antibiotics), but is well, it may well be correct to offer no additional treatment. However, do not take the statement 'Chronic Pseudomonas Infection' in the letter on trust; all letters must state date of last isolation and whether mucoid/non-mucoid. Check on EPR whether the child is a regular isolator (in which case treatment may well not change), or if the child has had several negative cultures over many months, in which case an attempt at 're-eradication' is made (see below). If in doubt, get out the previous culture results and discuss with the Consultant.

  - If the child is symptomatic, then the positive culture will guide choice of antibiotic treatment.

  - **First** isolations of an organism are always treated. Failure of eradication of 1st isolation ie, cultured after initial 3 months treatment, may be an indication for elective IV antibiotics or a course of nebulised tobramycin. This is a consultant decision.

- Isolations of *P aeruginosa* after six months or more of clear cultures are always treated. It is worth attempting 're-eradication' although likely the organism will persist. 1st line is oral ciprofloxacin for **3 weeks**. If resistant, we use a one month course of nebulised Bramitob, which can be extended to 6 months of alternating Bramitob/colistin (Consultant decision). If unwell, a 2-week course of intravenous antibiotics are given.

  It is important to arrange a follow up culture at the end of the course (local hospital or home care team can do this), and monthly thereafter for at least three months.

- Note that if the patient is still symptomatic or has a positive culture after an appropriate course of antibiotics, admission should be discussed with a consultant. We should not give endless oral courses; the use of more than two successive courses of oral antibiotics for the same exacerbation must be discussed with the consultant; but this is a different situation from the child who gets completely better, and a few weeks later has a 2nd oral course, from which they get better again.

1. ***Haemophilus influenzae***: Treatment dose augmentin for 1 month, which may be combined with azithromycin or clarithromycin; one further course of a cephalosporin can be given if no eradication/persistent symptoms. The sole indication for cefixime is proven *H influenzae* isolation in pure culture, with no response to first line antibiotics. However we try to avoid cephalosporins due to effects on encouragement of mucoid *P aeruginosa*.

2. ***Staphylococcus aureus***: treatment dose of flucloxacillin can go as high as 2g bd in the older children (consultant decision). For those repeatedly culturing *Staph* despite regular high dose flucloxacillin, consider other treatments, especially in older children. For example augmentin, fusidic acid or even rifampicin if this persists. MRSA is increasingly common. There may be some antibiotic sensitivities to guide you but in resistant cases, consider linezolid. Linezolid courses are for 14 days maximum because of the rare but documented risk of optic atrophy with longer courses. This is a consultant decision, and we would usually involve the consultant microbiologist as well.

3. ***Pseudomonas aeruginosa***:

- 1st isolation - **3 weeks** oral ciprofloxacin (or dual therapy intravenous antibiotics if unwell) **plus 3 months** nebulised colistin twice daily. We do NOT use 3 months ciprofloxacin because of concerns over resistance. We no longer routinely use gentamicin nebuliser unless there are also significant problems with *S aureus* or perhaps the 1st isolation is mucoid and resistant. The colomycin is used at double previous doses (see formulary).
- For 2nd and subsequent isolates unless there is a long interval between isolates (discuss with Consultant) - lifelong twice daily nebulised antibiotics, using double dose colomycin.
  (Note that for some nebulisers, only colomycin can be given, which may be entirely appropriate; also, that the first ever administration of a nebulised antibiotic should be in hospital, physiotherapists to supervise the trial).
- For children chronically isolating *Pseudomonas aeruginosa* and doing badly, consider rotating tobramycin and colistin nebulisers. First line choice of tobramycin is Bramitob (we use TOBI only if they have been receiving it before, or if the child is using an iNeb). But discuss this with Consultant.

- Aztreonam lysine for inhalation (Cayston) is licensed for adults only currently (Dec 2010). We might consider using it if TOBI and colomycin are no longer helping and chronic PsA infection is problematic in a child with severe lung disease. *Aztreonam lysine is not yet approved for use in children by Royal Brompton & Harefield NHS Foundation Trust Medicines Management Board (Dec 2010). PCT funding is required prior to initiation.*

- **Funnies and oddities**
  If detected at shared care hospital, please notify Brompton for advice. PLEASE ask the laboratory to send the strain of any 'oddity' for typing at Colindale. The local diagnosis is often wrong, because really experienced, CF specialist laboratories are needed to type unusual organisms. We have had catastrophes when a diagnosis of *Burkholderia cepacia* has been given by an inexperienced local laboratory, and the specimen/growth then destroyed before confirmation.

1. ***Multi-resistant gram negative*** **organisms** (any): get extended sensitivities and start long term oral antibiotic to which it is sensitive, e.g. trimethoprim, minocycline, doxycycline (if appropriate age). Choice of IV therapy should be discussed with consultant.

2. ***Stenotrophomonas maltophilia***: usually clears spontaneously and is frequently not pathogenic. However if symptomatic, treat with an oral antibiotic if one available. Antibiotic sensitivity testing is not always reliable for this organism, so co-trimoxazole is usually the best option. Can also use a 2-4 week course of chloramphenicol (currently a very expensive option - £400-1500 for 2 weeks), or trimethoprim, or minocycline if >12 years old (doxycycline may be used as an alternative as it is once daily – sensitivity to minocycline should imply sensitivity to doxycycline).

3. ***Burkholderia cepacia*** **complex**: this must be discussed with the consultant and will depend on sensitivities. Patients who become infected with BCC do not come to usual CF clinic, but are seen in general respiratory clinics. If they are on the ward, they are kept isolated in a cubicle for the whole admission. Nebulised meropenem or oral trimethoprim may be used for BCC.

4. ***Non-tuberculous mycobacteria (NTM)***: This includes a large number of species and the commonest to affect the lungs are *M avium complex* and *M abscessus;* others found include *M kansasii M xenopi* and *M malmoense*. When grown in the sputum of children with CF, they are usually there as commensals and have no significant effect on respiratory function or nutritional status. A single isolate is NEVER treated, and even a child with multiple isolates has a 50% chance of not being infected. However occasionally treatment is required (consultant decision). Antibiotic sensitivity testing is critical. See appendix II for detailed policy on treatment of NTM (joint with adult RBH unit). We routinely culture for it at annual review, Culture specifically for non-tuberculous *mycobacteria* on annual assessment visit, in a child who is unwell but culture-negative, on bronchoalveolar lavage, and on admission for an exacerbation; also when previously cultured.

5. ***Candida*** grown in sputum is inevitably from the mouth itself. Local treatment will be given if the child is symptomatic *i.e.* sore mouth, visible white plaques; using nystatin 100,000 units/ml 1ml swished around the mouth and swallowed QDS.

6. ***Influenza***. NICE guideline on influenza therapies (Feb 2003) state "when influenza is circulating, an at-risk child who presents with influenza-like illness and who can start therapy within 48 hours of the onset of symptoms is treated with oseltamivir". CF patients are clearly in this category and must be encouraged to see their GPs early for a prescription when there is a high flu incidence. This still applies to our patients who have had influenza immunisation. Oseltamivir (Tamiflu) (must be given for H1N1 influenza) is taken twice daily for 5 days, it comes as suspension or capsules and dosage by age/weight is in BNFc. Appropriate swabs (nasopharyngeal aspirate) should be taken for virus detection to confirm the diagnosis.

- **Choice of intravenous antibiotics.** This will depend on previous sputum results.

1. *No previous P aeruginosa* - must cover common pathogens including *S aureus, H influenzae, Moraxella catarrhalis* as well as possible first isolate of *P aeruginosa* (especially young infants). Start with meropenem (more gram positive cover than ceftazidime), tobramycin & high dose oral flucloxacillin.

2. *Chronic infection with P aeruginosa* – ceftazidime & tobramycin is 1st line unless previous sensitivities suggest otherwise. We routinely add oral flucloxacillin if *S aureus* is isolated within the last year. Flucloxacillin is usually given orally as it causes problems with IV lines and may cause backache.

3. *When to change antibiotics* – there is no evidence that *in vitro* sensitivities correlate with *in vivo* outcome. Therefore, if the child is improving on 'best guess' antibiotics, but the *Pseudomonas* comes back 'resistant', do NOT change drugs without first discussing with the consultant. If the child is not responding, a change may be indicated whatever the sensitivities – again, discuss with the consultant. If a change is made, do it at such a time that the CIVAS (Centralised Intravenous Additives Service) can be used to fill the new prescription (section 11.1c).

4. ***MRSA***- for 1st isolation in sputum/cough swab, we treat for 3 months with 2 oral agents, usually rifampicin plus fusidic acid or trimethoprim. Beware of hepatic toxicity. Vancomycin and teicoplanin are IV drugs active against MRSA. Teicoplanin does not require blood levels and is the preferred choice. The decision to treat chronic MRSA infection is a clinical one based on signs, symptoms and investigations, and should be in accord with hospital infection policy. Consider using linezolid, available orally and IV, when traditional agents fail (consultant decision). Check current Hospital Policy on the intranet; also remember surface decontamination protocols.

Further issues -

Aminoglycosides.

Due to safety and nephrotoxicity considerations, **tobramycin** is our 1st line aminoglycoside (we DO NOT use gentamicin), assuming the organisms are not resistant to it. This is based on its superior MIC and data suggesting that *P aeruginosa* is more often resistant to gentamicin than tobramycin.

There is evidence that once-daily dosing of aminoglycosides is less toxic and results in more effective bacterial killing than conventional three-times daily dosing. There is also evidence

that the incidence of *P aeruginosa* resistance to aminoglycosides may decrease with once-daily rather than three-times daily administration. In addition, less money is spent on equipment such as needles and syringes and importantly for the child with CF, there is a need for fewer blood tests because trough serum levels only need to be monitored. It also saves on nursing time for drug administration. The aminoglycoside regimen is now:

Amikacin	30 mg/kg once daily over 30 minutes
Tobramycin	10 mg/kg once daily over 30 minutes

The aminoglycoside should ideally be administered in the morning or early afternoon because there is a circadian variation in renal toxicity. We are doing levels 23 hours after the 1st dose, and it is given around 2pm, so levels are taken at 1pm.

Note that these are doses for CF patients ONLY; doses may need to be reduced in other situations.

You must know before you prescribe whether there has been a high trough level during any previous course – ask the family specifically, and search Electronic Patient Record for the information. If there has, the dose should be reduced by **20%** from the outset, and ensure the renal function is measured alongside any trough doses.

Measurement of trough levels

a) Serum aminoglycosides levels should be measured **23 hours** after administration of the **first** dose (i.e. 1 hours before 2nd dose), and also 23 hours after any adjustment. We repeat them weekly thereafter.
b) Serum urea and creatinine should be measured at the time of first cannula insertion and with each trough level. Occasionally it may be necessary to just use a finger prick for trough levels, in which case urea and creatinine can be omitted. They would have to be done though if the drug level came back high.
c) Levels should NEVER be taken through the same line that the antibiotic was given and that includes portacaths/longlines. Label blood form –'TROUGH'.
d) Aim for trough < 1mg/l for tobramycin, and trough < 3mg/l for amikacin. The result must be written on the drug chart and the next dose will not be given unless this is done.
e) If the trough is >1mg/l (or >3mg/l for amikacin) omit the next dose and check the trough level 24 hours after the omitted dose. Only once the trough level has fallen to below 1mg/l (3mg/l amikacin) can the patient be re-dosed, reducing the dose by 20%, and the trough level re-checked after 24 hours. Wait for this level to come back and only continue if level is <1mg/l (<3mg/l amikacin).
f) If the patient's renal function remains unchanged throughout the remaining course continue on the reduced dose and recheck the level weekly thereafter.
g) Peak levels are not done routinely but may be taken if there is concern about clinical progress on a reduced dose. This should be taken 30 minutes after the end of the infusion. Aim 20-30mg/l for tobramycin.
h) Each time levels are done, document in the notes:
   Date/time blood taken
   Dosage regimen
   Results (also on the drug chart)
   Any change to dosage
   Any other action taken

Consider measuring aminoglycoside trough levels at other time if –

- Dehydration
- DIOS
- Other nephrotoxic drugs e.g., ibuprofen.

Linezolid. A new class of antibiotic, an oxazolidinone, is available orally and IV. Oral bioavailability is 100% so IV preparations rarely required. It may be useful for *MRSA* or *Staph aureus* refractory to 1st line treatments. It is extremely expensive (up to £3,137/ month) and is available in the community. It can cause blood dyscrasias so full blood counts should be monitored weekly throughout treatment and there are now reports of optic neuropathy with courses >28 days. Therefore, linezolid should only be started on consultant approval and initially we will aim for 2-week courses. For those on prolonged (4 weeks or more) or repeated courses, ophthalmological assessment is mandatory and should be repeated every TWO months. Where possible patients should be warned to immediately report any visual changes, regardless of treatment duration.

Use of nebulised tobramycin (Bramitob or TOBI). In patients chronically infected with *P aeruginosa* who are gradually deteriorating, we will try nebulised tobramycin using the Bramitob® brand at a dose of 300mg twice daily on alternate months (TOBI® brand is used for patients on existing therapy or for use via an i-neb) – this is a consultant decision. We use Bramitob or TOBI and no longer the intravenous preparation. For the in-between month, the patients should receive nebulised colomycin at the usual dose for sole therapy. Children must have a bronchoconstrictor challenge organised with the physiotherapists when starting for the first time; the first dose of every nebulised antibiotic is given in hospital, with pre- and post-nebulisation spirometry. If bronchoconstriction occurs, use pre-dosing with a bronchodilator, and repeat the supervised challenge.

IV colistin. Occasionally we have used long term twice daily IV colistin (colomycin) for children unable to last even 3 months without 2 week courses of IV antibiotics. This is a consultant decision. See formulary for the dose - the usual total daily dose divided into 2 doses.

Drug doses. In general, high doses are required because of high renal clearance and also to ensure high levels of tissue and sputum penetration (see drug formulary section). Use the serious infection doses, and round up not down. Do not prescribe silly volumes e.g. 3.44 ml - the nurses cannot measure them accurately, and neither can you. CF is a serious condition and the aim of therapy is to push antibiotic doses to the upper therapeutic range. When results of sputum culture are available, confirm that all organisms are covered by the chosen regime. However, if the child is improving clinically on antibiotics to which the organisms exhibit *in vitro* resistance, do not automatically change them (but discuss with consultant). See section 11.1c for dose banding when using CIVAS.

Allergic reactions

In acute reactions, stop the infusion & give:

- IM adrenaline (<6 years 150 micrograms, 6-12 years 300 micrograms, >12 years 500 micrograms) – doses repeated if necessary at 5 minute intervals according to blood pressure, pulse and respiratory function).

- IV chlorpheniramine (<6 years 2.5mg, 6-12 years 5mg, >12 years 10mg), continued orally at usual doses for 24-48 hours to prevent relapse).
- IV hydrocortisone (<6 years 50mg, 6-12 years 100mg, >12 years 200mg), continued three times a day for 24-48 hours to prevent relapse.
- Monitor BP/HR/SpO_2/RR.
- Listen to the chest.
- Consider giving oxygen and a plasma expander.
- Document event clearly in the notes, and on allergy section of dug chart.
- Inform consultant.
- Make sure child and family know which is the offending antibiotic, and this information is written all over the notes and becomes part of that child's diagnostic list on letters and summaries.

The majority of allergic reactions are 'late onset' occurring many days after the antibiotic course starts; rather than a more immediate allergic reaction, which can take place within minutes of taking a drug. The late reactions may present in a variety of ways, often with non-specific features, including rashes, unexplained fevers, nausea, vomiting, diarrhoea, joint pain, muscle pain, lethargy, abnormal liver function results and abnormal haematological results. Management of these reactions is essentially to recognize them early and to stop the relevant drug, if it can be worked out which drug is causing the reaction. Improvement in symptoms should be seen within a few days.

Antibiotic desensitisation may be considered if the child has multiple antibiotic allergies. This can be undertaken with incremental introduction of the antibiotic at low dose, usually with prior treatment with systemic corticosteroids and antihistamines. If this is considered contact the pharmacy team at the earliest opportunity to discuss further.

Piperacillin/tazobactam (Tazocin, piptazobactam) is rarely used because there is a high incidence of allergy, and because of cross reactivity, patients may become hypersensitive to other antipseudomonal penicillins. It has also been recorded to cause reversible bone marrow suppression – thrombocytopaenia, neutropaenia.

Epipens

It has been advised by the CF Trust that all patients who receive the full course of IV antibiotics at home should have an Epipen. At Royal Brompton, we strongly advise the 1st dose is given in hospital. There are no references documenting anaphylaxis on second dosing of antibiotics when no reaction was observed after the first dose. Symptoms may still occur as a delayed reaction, sometimes 48-72 hours later, usually in the form of a maculopapular exanthema or urticaria.

There are however 2 case reports which record separate incidences in which adult patients previously not allergic to cefazolin have had anaphylactic reactions upon receiving their first dose on the second occasion.

The need for an Epipen cannot be completely excluded if the patient has not reacted to the first dose of the antibiotic, as delayed symptoms may occur later when the patient has been discharged. However these are generally mild in nature and may not require the use of an Epipen. In the UK, the practice of prescribing an Epipen to all patients having home IV antibiotics is not common

We must stress though that it is our practice and recommendation that **the 1st dose is always given in hospital** (see section 6.2b).

6.2b Home IV antibiotics

- Lack of bed space is not an indication for home IVABs.
- The first dose of both antibiotics should always be given in hospital.
- Any Parents/Carer wishing to undertake home IV therapy must be carefully selected and be discussed with the CF Nurse Specialist and Consultant before any decision is made.
- Families must be able to follow instructions provided, be fully aware of the treatment burden and be happy to carry this out. There is a training pack and the CF nurse specialists must be satisfied the parents are competent.
- Home IV therapy is optional and never compulsory Parents must **not** be pressurised (even if the child is anxious to go home) and must be happy to undertake the task. They must be confident of being able to continue with other aspects of the treatment i.e. extra physiotherapy and attention to diet.
- Families 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 (see below).
- Only exceptionally will families have every course of IVAB at home. On the discretion of the CF Consultant and CF Nurse Specialist, patients will usually have at least one (or part of) course of treatment in hospital per year.
- Antibiotics must be ordered before 3.30 pm the day before IVs are due to start therefore prescriptions need to be in pharmacy by 3.30 pm at the latest. Prescription pads can be found on Rose Ward, Outpatients and in pharmacy.
- Shared care doctors can fax over requests to 020 7351 8763 for the attention of the CF CNS or contact the Respiratory Registrar on call directly via the hospital switchboard.

Parents/carers must complete the home IVAB training booklet and be signed off in 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 Eclipse device (where applicable). This is the collapsible infusion device.

Please refer to training book for full details. This is available from the CF Nurse Specialists or Rose Ward.

Patients must have their 1st dose of antibiotics on Rose ward or their local shared care centre. Before discharge the following MUST be arranged:

- Consent and competency form should be signed and placed in the notes.
- Inform home care nurse/physio or local community service, local hospital team if applicable and GP.
- Aminoglycoside levels or Us & Es (if on Colistin) must be arranged and booked.
- Children are usually seen after the 1st week of IVABs in clinic or by the CF home care nurse or physiotherapist and at the end of the 2nd week in the clinic or on the ward, *before* the line has been removed.
- CF paediatric physiotherapy homecare team alerted and verbal contact or home visit arranged.

It has been suggested by the CF Trust that all patients receiving home IV antibiotics have an Epipen at home. See above.

6.2c 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 - usually 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. However the final decision has to be left to the surgeon. If the child 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 taken by surgeons. Investigations: CXR, full blood count, coagulation including thrombophilia screen, U&E, group & save. If the thrombophilia screen is abnormal, discuss with Paediatric Consultant and Haematologist.

When possible, children will commence intravenous antibiotics for 48 hours prior to surgery (this can be at home or local hospital). However if IV access is a big issue, then we would wait until the portacath is sited before starting IVABs.

Surgeon - Mr Michael Dusmet and Mr Simon Jordan will do older children (> age 5) at RBH, and we also ask Mr Simon Clarke, Paediatric Surgeon at Chelsea and Westminster Hospital, especially for the smaller children. A formal referral by letter to out-patients is usually made. Surgeons take consent for the procedure. Consider also whether a blind lavage or bronchoscopy should be performed at the time of anaesthesia to obtain material for culture; **also discuss with the paediatric consultant (Jane Davies or Andy Bush) as bronchoscopy, lavage and endobronchial biopsy may be performed for research purposes once consent obtained**. Physiotherapy is intensified for at least 24 hours before surgery. Patients will usually be admitted to RBH prior to surgery. Protocols currently variable, so check with CF Nurse Specialist.

Post insertion -

- Chest x-ray done for line position and pneumothorax.
- Analgesia - **Regular** paracetamol 20mg/kg (max 1 gram) 6 hourly +/- Ibuprofen 5mg/kg (max 400mg) 8 hourly **or** Diclofenac 1mg/kg (max 50mg) 8 hourly. Be wary of using ibuprofen when patients are taking aminoglycosides. Opiate analgesics may be required (Oramorph 0.1mg/kg every 4 hours) during the first day or so but a laxative should be given at the same time
- 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.
- Usually dissolvable sutures are used - check before patient goes home.
- There is some evidence that using the port to take blood samples increases the risk of line infection. This may be a difficult issue, because the child may have poor veins. Consider the use of fingerpricks where possible, and discuss with an experienced nurse specialist or Consultant.

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, local community paediatric nurses or local hospital. Families may eventually learn to do it.

- Local anaesthetic cream is used.
- Always use the proper needle (straight bevelled).
- Always use a sterile technique.
- 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 on-call consultant in paediatric cardiology. Remember that one of the commonest causes of pulmonary emboli in children is an endovascular foreign body. In a CF child with pleuritic pain and/or breathlessness and/or haemoptysis at least consider this diagnosis. V:Q scanning is a waste of time. Consider spiral CT with contrast or even angiography if this is a real possibility. Catheter fracture has been reported after a road traffic accident in a child wearing a seat belt.
- **Tinnitus** – at the time of antibiotic administration may indicate line migration into the neck veins passing cranially.

6.3 Corticosteroids

Indications for oral steroids:

- Allergic bronchopulmonary aspergillosis.
- Severe intractable bronchospasm / severe small airways disease.
- Long term use as an anti-inflammatory agent is contraindicated in most cases due to the adverse risk-benefit ratio.
- Terminal care – may act as general ‘tonic’.

We tend to use prednisolone which must **not** be enteric–coated otherwise absorption is poor in CF. Dexamethasone may also be used and anecdotally may be better for those whose behaviour/mood is adversely affected by prednisolone (NB *prednisolone 5 mg = dexamethasone 0.75 mg*). Dose regimen for ABPA is in section 6.7. For severe bronchospasm, dose is 2 mg/kg prednisolone administered in the morning after food, which will be reduced as soon as possible, depending on the response. We sometimes use intravenous methylprednisolone 10-15 mg/kg/day (max dose 1gm) for 3 days, repeated monthly – for severe cases and when compliance with oral prednisolone is an issue.

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 & polydypsia. Regular urinalysis for glycosuria is important, particularly in older children. Other problems are growth failure and hypertension (measure BP in clinic), less commonly oral candidiasis, cataracts and osteoporosis. Those on long term steroids will have DEXA scans at annual review. Exposure to chicken-pox in a child who has not yet had it, may require varicella-zoster immunoglobulin (see section on immunisations). If a child is on long term oral steroids itraconazole will usually be given in case there is exposure to aspergillus.

Indications for inhaled steroids

- Symptomatic wheezing that requires regular bronchodilators, in a similar regimen to BTS guidelines for asthma. Especially in atopic children. Ideally acute bronchodilator reversibility should be documented.
- Long term use as an anti-inflammatory agent in an asymptomatic child is probably not indicated. Although in theory it would seem useful due to the nature of the persistent lung inflammation, benefit has not yet been proven.

We use budesonide or fluticasone but not beclomethasone. Devices used depend on the age of the child, but nebulised steroids are rarely used. In older children, at low or moderate doses (<400 mcg/day budesonide, <200 mcg/day fluticasone) dry-powder inhalers (DPI) are most suitable. High doses of inhaled steroids are preferably given via a spacer device to reduce mouth deposition and potential systemic side effects. However there will be some older children for whom a spacer is unacceptable and then a DPI should be used. Use of a standard metered dose inhaler alone must be actively discouraged.

Side effects include slowing of growth although the destined final height is usually unaffected, oral candidiasis (so mouth must be rinsed after the dose, especially if using DPI) and rarely a hoarse voice. Always consider whether the dose can be reduced whenever the child is seen in clinic, or indeed stopped (results of CF WISE study).

Children with wheezing that does not respond to inhaled steroid prophylaxis, should be started on a twice daily **long-acting β_2-agonist**. Use either salmeterol (25-50 mcg bd via accuhaler or MDI/volumatic) or formoterol (6-12 mcg bd via turbohaler). The patient must be taking an inhaled steroid as well. We would normally use a combination inhaler (Seretide or Symbicort) to make it easier for the children.

6.4 RhDNase (Pulmozyme)

See shared care document for GP prescribing (appendix VII).

RhDNase (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 FEV_1 but this masks a wide response range from deterioration to marked improvement (over 20%).

Indications:

It should be a consultant decision to start DNase in all cases

- Traditionally an FEV_1 persistently <70% predicted *after optimisation of other treatments* in a sputum producing patient. We have now lowered the threshold and would expect patients to have DNase if their FEV_1 is <85%.
  - Check compliance, especially with physiotherapy; easy to say, difficult to do.
  - Exclude new infections e.g. *P aeruginosa, B cepacia, S maltophilia,* Aspergillus, NTM etc.
  - Exclude or treat allergic bronchopulmonary aspergillosis.

- We now have a low threshold for starting a child aged 6 years and above on it if they are having recurrent respiratory symptoms, whatever their lung function (even if it is 100%).
- It is still exceptional for us to give it to preschool children, but it may be warranted on occasions (mandatory consultant decision).

Other indications include.
- Difficulty in expectorating sputum because of a perceived severe 'stickiness'.
- Children who hardly expectorate at all but have symptoms.
- Persistent wheezing.
- Persistent or recurrent focal x-ray changes e.g. consolidation in a lobe or part thereof (consider bronchoscopy with instillation under direct vision – see section 6.10).

There is some evidence for prophylactic benefit as a trial of use in 6-10 year olds with near normal lung function showing a reduction in exacerbation rate and a halt in deterioration of lung function. A recent study showed no clinical difference in those receiving the drug daily or on alternate days. A further study showed a reduction in overall DNA with DNase use as a proxy for reduced inflammation.

Dose - Trade name: Pulmozyme 2.5mg by appropriate compressor and nebuliser ie, standard or faster E-flow or I-Neb (if using the I-Neb 1ml DNase is nebulised and the rest is discarded). After 3 months of daily therapy, usually given alternate days. A few patients prefer daily, as it is easier to remember.

There is **no need** in children to do a bronchoconstriction trial when first starting DNase – confirmed by manufacturer (adults do this however).

Timing - Traditionally given in the afternoon 1 hour before physiotherapy. However a study in older children and adults showed a modest overall improvement when given at bedtime (ie, 10-12 hours pre morning physiotherapy) with no nocturnal desaturation. We would prefer it is taken at tea time, but if that is too inconvenient, then on a case by case discussion it may be given before bedtime.

Involving the GP - This is an expensive drug (about £7500/year if used daily) and currently is prescribed by GPs. If a 3 month trial period has shown a benefit, most GPs will now prescribe it. If there is a problem the shared care guidelines (appendix VII) may help the GP to prescribe it. As a last resort continuing supplies are prescribed by the patient's local hospital or us.

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. If there is a response at 3 months to daily treatment, we usually switch to alternate day administration. If there is subsequent deterioration, the dose can be increased to daily again though this has not actually been necessary so far.

Side effects: rare and mild; hoarse voice occasionally and rash sometimes seen. There is no need to stop its use in patients with haemoptysis or pneumothorax

6.5 Hypertonic Saline

Hypertonic saline (HS) can be used in the short term to induce sputum in patients in who repeated upper airway cultures are negative or as part of their admission physiotherapy package; it also has a role for long term at home. HS can cause bronchoconstriction, so pre-treatment with a bronchodilator should always be done, and the first dose should always be given with spirometry before and afterwards (the physiotherapists usually arrange this). In all cases, HS is given immediately before physiotherapy (in comparison to rhDNase which is given a minimum of 1 hour before physio). If HS cannot be tolerated, lower concentrations may be considered. We now use ready 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 over age 6 years who has a rattly cough, and is not doing well, but does not expectorate sputum spontaneously, we use 3.5% saline ('normal' saline is 0.9%). To achieve this concentration dilute 2 mls 7% hypertonic saline with 2 mls water for injections. This should be combined with vigorous physiotherapy.

If HS is to be used as an adjunct to physiotherapy, 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. If HS is being contemplated for a ward patient, discuss with physiotherapy first.

The first line mucus clearance agent is rhDNase, but our data show that a third of rhDNase non-responders increase their lung function with HS. The longer term Australian study showed clinically trivial improvements in lung function, but fewer infective exacerbations with HS. The down side is two more nebulisers per day, which may not be feasible, especially if the child is already taking nebulised antibiotics. HS long term is therefore considered on an individual basis, especially for those with many infective exacerbations, who have not done well on rhDNase. See also the new section on Mannitol.

Frequently asked question: will it work the same if I make up my nebulised antibiotics with HS 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.

6.6 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. To date, two published trials and the pilot data from a large multicentre Phase 3 study suggest that it may improve lung function in some patients with CF. A NICE review of the role of inhaled mannitol in children with CF is due for publication in 2011. Children who do not respond to rhDNase and fail to respond to, or tolerate, hypertonic saline (HS), may warrant a trial of inhaled mannitol.

Currently dry powder mannitol is packaged in gelatine capsules and delivered via a specific dry powder inhaler device. All patients are pre-treated with bronchodilator 15 minutes prior to

administration. As with rhDNase, there appears to be marked individual variation in response to mannitol. In addition, cough and bronchoconstriction limits its tolerability in some patients with CF. Given this, therapeutic trials on individual patients with a formal airway challenge prior to commencement of treatment are probably wise.

Inhaled Dry Powder Mannitol is not currently approved by Royal Brompton & Harefield NHS Foundation Trust Medicines Management Board (Dec 2010). Treatment should only be initiated by a Consultant.

6.7 Long term azithromycin

There are two main uses of azithromycin:

a) As a conventional antibiotic (see section 6.2a) for treatment of respiratory infections especially if Mycoplasma or Chlamydia are being considered.
b) As a long term anti-inflammatory agent, although it's mechanism of action is unknown. Studies show improvement in FEV_1 (median 5.5%) and reduction of oral antibiotic usage. It is believed to be effective in those with and without chronic *Pseudomonas* infection.

Criteria for long term use: Very similar to those for rhDNase (section 6.4) and should include those not benefiting from a 3 month trial of rhDNase.

Dosage: 250 mg once daily (<40kg) or 500 mg once daily (≥40kg)**.**

Judgement of response: Onset of action is slow (at least 2 months) and a minimum 4, preferably 6 month trial is required. If there has been a beneficial response then we recommend reducing the dosing frequency to Monday/Wednesday/Friday only.

Side Effects: Theoretically liver function abnormalities and reversible tinnitus although only one transient LFT abnormality was observed during the study. Liver function tests should be performed at any time blood is being taken for other reasons and at annual assessment. Use of azithromycin **and** erythromycin (prokinetic) long term should be avoided due to potential additive side effects

When AZM is started, prophylactic flucloxacillin is continued; but prophylactic augmentin may be stopped, unless the patient is known to have macrolide-resistant *H influenzae* (which is becoming increasingly common).

6.8 Aspergillus 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 large number of manifestations in CF. In general, children are advised to avoid mucking out stables, and if they insist on horse riding this must be done out in the open.

1. **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 x 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 at a dose of 2mg/kg/day for 2 weeks, then 1 mg/kg/day for 2 weeks, then 1 mg/kg/alt day for two weeks. 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 10-15 mg/kg ONCE per day for 3 days every month, maximum dose 1gm [J Cyst Fibros 2009; 8: 253-7]. Decision to use should be discussed with the consultant.

Itraconazole is used routinely for treatment of ABPA, in combination with oral or intravenous corticosteroids. Our own study shows that at usual doses no child had recordable blood levels. For this reason we are giving the standard daily dose twice rather than once daily. For patients <12 years give 5mg/kg **bd** (max 200mg bd)**,** or >12 years 200 mg **bd** orally (monitor liver function) and continue whilst they remain on steroids. The capsules particularly are poorly absorbed so take these 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.

Stop ranitidine/omeprazole if possible to improve absorption. Liver function tests should be performed if blood is being taken anyway for repeat ABPA markers, otherwise do them for prolonged courses e.g. at least after 1-2 months or if there is a history of liver dysfunction (see BNFc for recommendations). NB. It should also be given to anyone taking oral steroids (for whatever reason) if there is any suggestion of concomitant aspergillus infection while they are taking the steroids. Beware of drug interactions e.g., with rifampicin, omeprazole.

Itraconazole levels

- Random sample should be taken after patient has been taking for at least 14 days (usually taken at the last bloods prior to discharge)
- Range: 5-15mg/L
- 1ml of serum into clotted blood vacutainers (Brown)

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. A recent audit of itraconazole in children at RBH showed that many patients on the lower dose of itraconazole (5mg/kg OD – max 200mg) did not attain therapeutic levels. Therefore, before changing to voriconazole in patients who did not respond to itraconazole, check to see if the itraconazole level was therapeutic (5-15mg/L). If not consider increasing the dose first. Voriconazole is expensive (~£1-3000/month) and can be prescribed by most GPs. Voriconazole should only be started with consultant approval. Regular (monthly) 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

- Pre-dose sample may be taken after patient has been taking for at least 3 days
- Range: 1.3 - 5.7mg/L
- 1ml of serum into clotted blood vacutainers (Brown)

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 (it tastes awful). If it essential to use it, and the child does not tolerate the normal 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. IV caspofungin can also be considered as 3rd line. These options are expensive and inconvenient, and their use is a consultant decision. The anti-IgE monoclonal antibody omalizumab may rarely be considered; this is a consultant decision and funding application to the PCT will be needed.

2. 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 neutropaenic 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. IV caspofungin can also be considered as 3rd line.

- Repeated positive sputum cultures in a chronically symptomatic child, also the child with IgE > 150 and. aspergillus RAST > 17.5. Also, there may be more exacerbations in children with chronic aspergillus infection. Consider itraconazole for one month or longer (consultant decision). Nebulised amphotericin is occasionally needed. Recent observational data have suggested that sensitised children (defined as above) MAY have better preservation of lung function if anti-fungals are prescribed. So consider this therapy if there is aspergillus sensitisation or positive cultures, even if asymptomatic.

- Mycetoma is rarely seen in CF but has been described. Suspect if halo sign in a cavity and 6-8 positive IgG precipitin lines. Confirm with CT. Treatment individualised - too rare to offer guidelines.

- Others: Amyloidosis is a late, incredibly rare and ominous complication of ABPA and sometimes CF alone. It should be considered if the following occur: proteinuria with oedema (nephrotic), goitre, hepatosplenomegaly not due to CF liver disease.

Indications for intravenous liposomal amphotericin

- Proven invasive aspergillosis
- Severe, chronic and persistent other aspergillus lung disease (including ABPA), with multiple side effects from conventional steroid therapy. This is a consultant decision only.

6.9 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 haemetemesis. 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. Please contact us. This occurs in 1% patients/year. The usual site of bleeding is tortuous bronchial arteries. In CF haemoptysis, remember the possibility of pulmonary embolism if the child has a portacath (see above). 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 child is taking NSAIDs, stop them. Consider stopping hypertonic saline if massive haemoptysis if the HS 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 -

- Give blood and correct coagulation defects if necessary (IV vitamin K/ FFP / cryoprecipitate).
- Start intravenous antibiotics; high dose oral *S aureus* cover must be part of the antibiotic regimen, irrespective of previous culture results.
- Continue with gentle regular physiotherapy, but omit chest clapping for 24 hours. This is essential and contact our physiotherapists for advice.

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 - the paediatric dose is 0.3 units/kg (maximum 20 units) over 20 minutes followed by 0.3 units/kg/hour (maximum 1 unit/kg/hour) continued for 12 hours after bleeding has stopped and gradually withdrawn over 24-48 hours (maximum duration 72 hours). It can lead to water intoxication and can cause bronchoconstriction. **IV terlipressin** (for children >12 years) has fewer side effects; dose (from BNFc) is 2mg then 1-2mg every 4-6 hours until bleeding is controlled, (maximum duration 72 hours); this is used by the adult unit.
- **Bronchoscopy** - It is rarely useful in the acutely bleeding child. If you are considering this procedure initially try flexible, then consider a rigid, under general anaesthetic. With massive haemoptysis, go straight to rigid bronchoscopy. This can be technically very difficult but may allow clot removal (beware precipitating further bleeding), tamponade of bleeding site using a Fogarty catheter, or haemostasis with thrombin glue or iced saline lavage/vasoconstrictor lavage.
- **Selective bronchial angiography and embolisation** can only be carried out by experienced specialists in a tertiary centre. 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. This is not a cure and many patients develop new vessels within months or years that may bleed and so require further embolisation.

- **Oral tranexamic acid** has been used long term in recurrent bleeders with some success. Dose is 15-25 mg/kg tds (max 1.5 g/dose).
- **Lobectomy** may be considered as a last resort.

6.10 Pneumothorax

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

Please contact us. 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 SpO_2 and give oxygen (check for CO_2 retention).
- Intercostal chest drain.
- Local anaesthesia and subsequent oral analgesia.
- Antibiotics (IV antibiotics are prudent in all but the most trivial pneumothoraces).
- Gentle physiotherapy must be continued, techniques and adjuncts may need changing (no PEP masks or IPPB). Deep breathing with inspiratory holds is encouraged. Please discuss this with the senior physiotherapist at Brompton.
- If the child is using BiPAP, this is a difficult dilemma, and BiPAP may need to be withheld temporarily. Seek senior physiotherapy and medical advice.

The lung may be slow to re-expand and if after three days there are no signs of resolution with a continuing air leak, then consult with surgeons (discuss with the paediatric consultant first). Surgery should be considered if no progress is being made. In some centres there is 50% mortality if a patient has a chest drain for more than one week. Similarly, recurrences are common (>50% ipsilateral and up to 40% contralateral) necessitating surgery. Sclerosing pleurodesis or pleurectomy make subsequent transplant very difficult although are not an absolute contraindication to future transplantation. Localised abrasion pleurodesis +/- surgical resection or thoracoscopic stapling of blebs lead to less adhesion so are preferable options, unless transplantation is never going to be an option (which is rarely the case). Pleurodesis is recommended for first ipsilateral recurrent pneumothorax.
No spirometry for 2 weeks after resolution.
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

6.11 Intractable wheezing / severe small airways disease

At least 50% of CF patients are atopic on the basis of skin prick testing to common allergens, although if aspergillus is excluded the prevalence of atopy is the same as that of the non-CF population. The great majority are well controlled with conventional 'asthma' type treatment using standard BTS guidelines for asthma.

In contrast, the foregoing discusses a small group of patients characterised by -

- Little if any sputum production (despite large amounts in the chest).
- Wheezing.
- Tight chest.
- A severe obstructive lung function pattern.
- Little if any bronchiectasis on CT scan.
- Often but not always IgE >500 iu/l.
- May be more common in girls.

These children should not be managed without consultant input as they pose an extremely difficult management problem and would also compulsorily fall into the category requiring a 'challenging CF protocol' (see section 6.12).

Particularly ominous is the patient who used to be a 'conventional sputum producer' who quite suddenly stops producing and begins to wheeze. There is no research on this subject so all suggestions are empirical.

- Check compliance, no physiotherapy equals no sputum.
- Is there ABPA? This is the most common and conventional explanation.
- Is there *Aspergillus fumigatus* in the sputum?
- Is there a new bacterium in the sputum- including Non-tuberculous mycobacteria?
- Is there an obvious atopic history (not just skin testing) for example animals, HDM etc?

If these all negative:

- Consider CT scan to assess structural damage / bronchiectasis (including expiratory views).
- Consider bronchoscopy and pH study.
- Consider an oral glucose tolerance test or better still a CGMS test (continuous glucose monitoring system).

Treatments –

- Begin **long-acting β_2-agonist** (salmeterol or formoterol). If >6 years formoterol (Oxis) via a turbohaler is preferred because it is a pure agonist. Under consultant supervision, doses can be empirically increased. Watch for side effects (tremor, palpitations etc.) then cut back. There are risks of hypokalaemia so serum potassium should be checked if high dose is to be continued (bananas are rich in potassium). There is also a theoretical risk of lengthening the cardiac QTc interval and an ECG should be considered after 2 weeks therapy (note - we have never seen a case). Symptomatic benefit must be proven and home peak flow or FEV_1 monitoring considered.

- **Symbicort** (budesonide/formoterol combination) can be used regularly with extra 'as required' doses administered through the day. Maximum we recommend is 400/12 twice daily with 4 extra doses of 200/6 allowed per 24 hours.
- Increase **inhaled steroids** to 800 mcg twice a day equivalent dose of budesonide.
- Consider using short acting β2 agonists, 10 puffs 3-4 times a day via a spacer.
- Consider slow release theophyllines e.g. Slophyllin – see BNFc for doses. Consider also IV aminophylline for an in-patient with severe wheezing.
- Consider a trial of Montelukast.

If above fails after 2-4 weeks:

- **Prednisolone** 2mg/kg/day in the morning for 14-21 days then review. If successful then try to wean over two weeks to 1mg/kg alternate days.
- **Pulsed methylprednisolone** can also be considered 10mg/kg once a day (maximum 1 gm/day) for 3 days (3 doses in total) and this can be repeated weekly in severe, intractable cases.

If there are persisting problems, consider alternative diagnoses again (ABPA, new bacteria) and ensure bronchoscopy, pH study CT chest scan and CGMS have been performed. In this situation, or if the patient is better but with unacceptable steroid side effects consider:

- **IV immunoglobulin** therapy e.g. Flebogammadif 5%. Dose 1g/kg over 16 hours on two successive days then 1g/kg on a single occasion each month. Trial should last 6 months. Benefit not usually seen till 3 months. Bloods should be taken before each dose for IgG, IgA, IgM, IgE and liver function tests; IgG subclasses should be measured before initiation of the regimen. Before initiating therapy, patients undergo bronchoscopy with biopsy, pH study & CT scan and CGMS unless recently done.

  As part of the DoH Demand Management Plan, we are now required to obtain confirmation of funding from the individual patients PCT **and** approval from the trusts and / or local hospitals Immunoglobulin panel **before** initiating treatment. Where IV immunoglobulin therapy is being considered contact the pharmacy team as soon as possible, as this process can take weeks to months.

  NOTE: Pre-treat patient before **EACH AND EVERY** dose with antihistamines (e.g. cetirizine or chlorpheniramine) and IV hydrocortisone as Flebogammadif 5%, especially the first dose, can activate complement with impressive side effects (severe headache, flushing etc.).

- **Azithromycin.** No special evidence but 250mg/day if <40kg or 500mg/day if >40kg given daily for six months may be beneficial although the effect may take at least 2 months to be seen.

- **Subcutaneous terbutaline** has also been occasionally very successful. Dose is 2.5 mg/day (5ml) of the intravenous preparation rising over 7 days to 5mg/day (10ml) to avoid side effects, and occasionally up to 10mg per day. We use a Thalaset needle and a Canè Crono ambulatory infusion pump. Treatment must be started as an in-patient. Potassium depletion does not appear to happen; side effects tend to be local soreness/bruising around the needle site. It has been used with little psychological harm in

children as young as 8 years but it does require careful management. Our asthma nurse specialists must be involved in setting this up.

- **Methotrexate**. Has been used in a few patients but response is often disappointing. The dose is given **ONCE A WEEK**, on the same day of the week. The standard dose is 10 mg/m^2/week and this dose is reached gradually over a number of weeks. Increments are usually 2.5 mg, which is the strength of 1 tablet (it also comes as 10 mg tablets). A 3-month therapeutic trial is undertaken. Higher doses would only be considered if benefit is proven but the patient is still not quite right. Higher doses are inappropriate if no response is seen at the standard dose. Folic acid 5mg is given 48 hours after the Methotrexate and regardless of the methotrexate dose

  Bloods are taken weekly for FBC, LFTs, electrolytes & creatinine, once stable on the maximum dose they can be done monthly. All prescribers must complete the 'Methotrexate Patient Held Monitoring and Dosage Record' when initiating therapy and monitoring treatment (kept in Paediatric outpatients). The consultant who initiated the therapy must be identified in the book and take full responsibility for dose changes and the course of treatment. This booklet contains information about methotrexate treatment, doses and blood results, and must be retained by the patient. This booklet should be bought to all appointments where therapy is being reviewed. Always check for drug interactions (see BNFc).

- **Voriconazole.** An orally active antifungal with much better absorption than itraconazole, which should be tried before IV liposomal amphotericin for resistant ABPA (see below). A recent audit of itraconazole in children at RBH showed that many patients on the lower dose of itraconazole (5mg/kg OD – max 200mg) did not attain therapeutic levels. Therefore before changing to voriconazole in patients who did not respond to itraconazole check to see if the itraconazole level was therapeutic (5-15mg/L). If not consider increasing the dose first. For dosing see drug section but a 4 to 6 month course may be required and it is very expensive (£1000-3000/month) and highly photosensitising.

- **IV liposomal amphotericin** (Ambisome). Consider with resistant ABPA (see relevant section) but also tried in children where no current formal criteria for ABPA are present (though have certainly had it in the past) but aspergillus continues to be grown. Entirely empirical theory is that ABPA does not occur if there is no Aspergillus present.

  Test dose 100mcg/kg (max 1mg) over 10 mins. Observe for 30 minutes. Then dose is 1mg/kg once a day rising to 5 mg/kg/day over 3 days and continue for about 4 to 6 weeks. Measure renal and liver function at least 3 times a week initially especially if other IV drugs are being given - one case of transient renal failure already. **Caution when used simultaneously with IV colomycin, or aminoglycosides** (risk of renal failure).

- **Omalizumab** (Xolair) (see ABPA section). If there are no formal diagnostic criteria for ABPA, but IgE is raised (although <1500 iu/ml) and other measures have failed then there are some case reports of it helping. Subcutaneous injection every 2 to 3 weeks depending on IgE level. As unlicensed for this indication, PCT funding must be confirmed before starting treatment.

6.12 'Challenging CF' protocol

In a similar way to how we use the multidisciplinary team to thoroughly assess children with difficult asthma, we now have a protocol for assessing CF children whose clinical state is a cause for concern. This may relate to any aspects of their CF condition. A decision to enter a child into the programme will be made by the named consultant at our weekly MDT meeting, after either a clinic visit, hospital stay, home visit or communication from the local team has suggested the child may require this. The consultant will then explain the procedure to the child and carers in clinic, and a letter will be sent to the family.

Typically children will fall into one of these categories -

- Any child whose lung function is more than 2 Z-scores below the published CF specific charts [Am J Respir Crit Care Med. 2005; 172: 885-91].
- Any child who receives $\geq$ 3 courses of intravenous antibiotics annually (whether planned electively or unplanned).
- Any child requiring home oxygen (almost invariably they will have been assessed in the protocol long before this stage).
- Any child in 'nutritional failure' – BMI < 2 Z scores below the mean; drop in weight or BMI centiles by 10% over a year.
- Any child with a severe CF pulmonary complication, e.g. massive haemoptysis, pneumothorax, therapy-resistant ABPA, or other cause of severe steroid dependency.
- Any child whose self or parent-reported symptoms are significantly different to what a clinician would expect (either overestimated or underestimated).
- Any child in whom there is refusal or extreme reluctance to give prescribed treatment by the carers.

Below are some of the likely causes with potential ways of assessing them. Some causes may be specific to respiratory or nutritional aspects, whilst some will be relevant to both and be more generalised.

1. Generalised

- *Non-adherence to therapy.* We need to obtain objective data where possible. This may include:
    - GP prescriptions picked up
    - home visit to check medications (where stored, whether still in original wrappings, how given, knowledge of medications, expiry dates)
    - physiotherapy knowledge of techniques they are expected to know and have been performing
    - down-loading data from nebulisers about usage
    - blood levels if on prednisolone, theophylline; consider also if on itraconazole, and especially voriconazole
- *Adverse environment*
    - passive or active smoking (urinary cotinine)
    - allergen exposure (RAST and skin tests)
    - assess home environment, including nebuliser cleanliness (esp. if ABPA the issue)
- *Psychological issues* which may be part of non-adherence, but have a far more complex role in chronic disease. Clinical psychology involvement is critical.

- *Social challenges* in the family preventing optimal care; these are numerous but may include financial problems, difficulties with the child's siblings, marital/relationship problems, ill health of a parent etc. A sensitive assessment to look at the family's strengths and challenges is necessary.

2. Nutritional (see sections 7.3, 7.4)

- *Significant undiagnosed co-morbidity*
  - Gastro-oesophageal reflux (pH study, GI referral if any doubt)
  - Impaired glucose metabolism - see Nicola Bridges to assess need for CGMS, OGTT (see section 8.1)
  - Electrolyte abnormalities – measure urinary electrolytes
- *Malabsorption* - basic GI screen including food diary, 3-day faecal fat, coeliac screen, ESR, and GI referral if still an issue.

3. Severe CF lung disease

These can be crudely split into two types, although there is often overlap.

- *'Distal and dry'* – These children are often tight and wheezy with little or no sputum production; treatment can be difficult & is outlined in section 6.11. Typical investigations will include ABPA markers, CT chest scan and bronchoscopy with pH study. The child usually has distal airway disease with air trapping on inspiratory and expiratory CT scans, and dry airways on a bronchoscopy. Gastro-oesophageal reflux must be excluded. Bronchodilator reversibility & lung clearance index will also be assessed.
- '*Pan-airway and productive'* – the child who has bad proximal bronchiectasis and marked purulent airway secretions. CT scan will reveal extent of bronchiectasis. Bronchoscopy will confirm the wet airways, and extensive microbiological assessment is necessary. This must include anaerobes, NTM, & unusual gram negative rods. Treatment may involve rotating nebulised antibiotics, 3-monthly intravenous antibiotics, long term macrolides, mucolytics, and different physiotherapy techniques.

  Typical investigations for worsening lung disease may include:
  - Bronchoscopy
  - pH study
  - CT scan
  - Formal lung function
  - Bronchodilator reversibility
  - Exercise testing
  - Lung Clearance Index
  - Overnight SpO_2 and $TcCO_2$
  - CGMS
  - ENT evaluation ± imaging, with ENT opinion
  - Physiotherapy assessment

Protocol -

Step 1: Multidisciplinary assessment at a separate visit (day case), not part of the busy routine clinic. They will see nurse specialist, physiotherapist, dietitian (who will provide a home food diary), psychologist, and pharmacist (who will contact GP and local hospital pharmacist for details on prescription uptake). Allergy tests may be done, either skin prick tests or RASTS if

blood testing is planned. Urinary cotinine levels will be measured. If appropriate they will be seen in ENT outpatients.
Step 2: A home visit jointly by nurse specialist and physiotherapist using a proforma. This will happen twice, with the child present on the second occasion only. This may be arranged for the same day.
Step 3: There will be a detailed assessment of the information to date and depending on the results, an admission may need to be planned.
Step 4n (Nutritional): 3 day admission. Nicola Bridges to see with sugar results in clinic, GI referral after the admission if no diagnosis.
Step 4r (Respiratory): Overnight admission for inspiratory and expiratory CT scan, LCI, bronchoscopy and pH study.
(If appropriate, the respiratory and gastrointestinal steps can be combined in one admission)
Step 5: Review of all the above with the named consultant and formulation of action plan with the child and family. This will be preceded by a full multidisciplinary review of the above, similar to that at the severe asthma meeting.

6.13 Bronchoscopy

Indications in CF:

1. Need for microbiological diagnosis in a non-sputum producing child:
   - Not responding to IV antibiotics.
   - Not previously infected with *P aeruginosa* in whom there is clinical concern due to persistent deterioration (do not simply start empirical antipseudomonal therapy).

     A cough swab / sputum sample must be taken on the same day prior to the bronchoscopy.

2. Therapeutic suctioning:
   - Persistent focal area of collapse / consolidation on chest x-ray, may also include instillation of rhDNase (2.5 mg in 10 mls 0.9% sodium chloride (normal saline).
   - It is rarely of value when chest x-ray changes are generalised.

3. Newly diagnosed patients (including newborn screened):
   - Please see section 5.4.

4. Other indications:
   - Intractable wheezing to exclude bronchomalacia.
   - Lavage for fat-laden macrophages to exclude aspiration.
   - Persistent defect on isotope ventilation scan.
   - Lung function or LCI lower than expected (previously assumed due to technique).
   - Haemoptysis may occasionally require rigid bronchoscopy.
   - At the time of a general anaesthesia for another procedure.

Bronchoscopies are performed on Monday or Friday afternoons in Theatres, booking for in-patients is done through bed managers. Bookings for out-patients who are to be admitted are through the Bed Manager (bleep 1234). The bronchoscopy health care assistant (HCA) must also be informed.

They are all done under general anaesthesia, and often patients will have had no antibiotics prior to the procedure but require minimum 48 hours IVABs after if significant secretions are seen. In practice bronchoscopy is often done at the start of a 14 day IVAB course when the patient is not doing well and no microbiology is available or nothing is ever grown. For newly diagnosed newborn screened babies, if the bronchoscopy is clear they need not stay afterwards for IVABs.

No other preparation is required, but a procedure-specific consent form must be signed. Patients must have no food for 6 hours and clear fluids up to 2 hours before the procedure.

It is often useful for a physiotherapist to be present during the procedure. Sometimes rhDNase may be instilled down the bronchoscope suction channel to a localised collapsed area that is obstructed by thick mucus. The dose is 2.5 mg in 10 mls 0.9% sodium chloride, and then a small amount of air is instilled down the bronchoscope to ensure no drug is left in the suction channel.

Bronchoalveolar lavage fluid is sent to microbiology for culture (including NTM, fungi), virology for immunofluorescence, and cytology for fat-laden macrophages. Protocol is to use 3 aliquots of 1ml/kg lavage, usually from right middle lobe or lingula, although other areas will be lavaged in addition when indicated.

All CF patients undergoing bronchoscopy must be discussed with Dr Jane Davies or Prof Andy Bush re inclusion in research studies.

6.14 Chest physiotherapy

A paediatric physiotherapist is available in clinic to assess all patients and discuss/review their physiotherapy management. The airway clearance techniques (ACT) used vary within age groups and are always assessed on an individual basis:

- **Babies and infants**– Techniques taught may include modified gravity assisted positioning, intermittent chest clapping and blowing games; as well as infant positive expiratory pressure (PEP), assisted autogenic drainage (AAD) and age appropriate exercise.
- **3-4 years and upwards** – Progression to Active Cycle of Breathing Technique in modified or gravity assisted positions. Positive Expiratory Pressure (PEP) and other oscillating PEP devices may be introduced. Exercise is also strongly encouraged but does not usually replace ACT.
- **8 years and upwards** – Encourage more independent treatments using a full variety of airway clearance devices and techniques as appropriate (with family support /supervision). The importance of exercise is again re-iterated.

The frequency and duration of treatments will alter depending on infective exacerbations, severity of disease and individual circumstances. In the majority of cases twice a day for 10-15 minutes is the minimum recommended.

Airway clearance techniques taught include:

- **Active Cycle of Breathing Techniques** (ACBT) – Combination of thoracic expansion exercises, breathing control, and forced expiration techniques.
- **Positive Expiratory Pressure** (PEP) – Provides resistance to expiration through a mouthpiece or facemask, followed by forced expirations. Can be used in conjunction with ACBT.
- **Flutter®**– Pipe-shaped device that creates oscillation and positive pressure on expiration used in conjunction with forced expirations and ACBT.
- **Acapella Choice® -** Green device with a mouthpiece that creates oscillation and positive pressure on expiration. Used in conjunction with forced expirations and ACBT.
- **Modified Autogenic Drainage (AD) –** A three phase breathing regimen utilising high expiratory flow rates and variable lung volumes to unstuck, collect, and evacuate secretions.

***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 and appropriate exercise advice is given.
- **Posture** - Assessment, education and treatment is provided.
- **Urinary incontinence** – Stress incontinence can occur even in young children during activities such as coughing, laughing and exercise. Please consult the physiotherapist for advice.

Inhaled medication should be co-ordinated with physiotherapy:

- Bronchodilators -10-15 mins pre-physiotherapy if necessary and benefit shown.
- Hypertonic Saline - Immediately pre-physiotherapy but post bronchodilator.
- RhDNase – At least 1 hour pre-physiotherapy. N.B some children take it 1-2 hours pre-physiotherapy and a few even longer, but do *not* take immediately before bed (unless it has been agreed by the CF consultant).
- Steroid Inhalers – Usually taken post physiotherapy treatment.
- Nebulised Antibiotics - Post-physiotherapy. Breath assist jet nebulisers' or other appropriate nebuliser systems should be used (see below).

For inhaled antibiotics and hypertonic saline the child must always be assessed for bronchoconstriction when the 1st dose is given. This should be done in hospital and requires the patient to perform pre and post dose spirometry. The following equation is useful to work out % constricted (> 10% is significant):

$$\frac{\text{Pre } FEV_1 - \text{Post } FEV_1}{\text{Pre FEV1}} \times 100 = \%\ \text{bronchoconstriction}$$

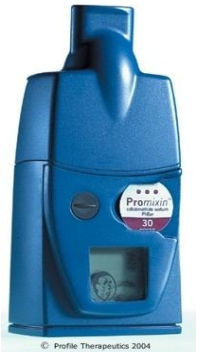
If the child cannot perform spirometry then they should be observed having their first dose. SpO_2 and auscultation findings should be monitored throughout the test.

The Physiotherapy Department provides a long-term home compressor and nebuliser service for patients under the care of Royal Brompton Hospital. For those patients under shared care,

appropriate contact will be made regarding treatment modifications required or community visits can be arranged.

There are alternative nebuliser delivery systems available such as the Pari eFlow Rapid® and I-neb®. The Royal Brompton Hospital has a limited supply of both devices. The Pari eFlow Rapid® can also be purchased privately, while the I-neb® can be obtained if promixin® is prescribed by the patient's GP. These devices may not be suitable for all patients so it is important to get advice from the physiotherapist.

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
• 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 FEV_1>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	• Can only be used if can inhale through mouthpiece (>2 years) • Only available if on Promixin® • Promixin ® generally prescribed by GP - more expensive than colomycin ® - £1295 per year more than equivalent colomycin (even though ½ strength required i.e. 2MU Colomycin ® = 1MU 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 (= PARI LC PLUS ®) – ?longer Rx time • Can't nebulise Bramitob through the I-neb® • Some medications may taste stronger

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

Colistin Dose	**Conventional Compressor**	**I-neb® - Promixin®**
2 MU	2MU	1MU (mix with 1ml saline)
1MU	1MU	1/2 MU (mix 1 MU vial with 2mls saline, draw out 1ml Discard remaining solution.

Note that when someone changes from colomycin + gentamicin combination to colomycin alone, we would give double the colomycin dose in a standard nebuliser. This dose then has to be halved if Promixin is used.

Of course if they are already on colomycin alone, then if they start Promixin the dose is halved.

CHECK WITH A PHYSIO IF YOU ARE UNSURE.

Example 1 - Child taking colomycin 1MU + gentamicin 80mg by standard nebuliser. Doubling dose of colomycin to 2MU (as stopping gentamicin), means actually give 1MU by I-neb.
Example 2 - Child taking colomycin 2MU alone by standard nebuliser. Give 1 MU by I-neb.

Tobramycin 300mg/5mLs and hypertonic saline 7%/4mLs can be nebulised through the I-neb®. The table below may be useful to work out dosage 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®

PROS	CONS
• Fast nebulisation: TOBI ® 6-8 mins, Colomycin ® 3-4 mins, hypertonic saline and rhDNase 2-3 mins • More durable than I-neb® • Any drug (2-6 mls) can be used • Virtually silent and lightweight • Battery or multi-volt power • Can be used with all ages (mask or mouthpiece)	• £495 plus at least £93 replacement parts annually (2009 price list) • Not 'breath activated' • As continuous, some drug is wasted in expiration • Medications may taste stronger • Antibiotics require filtering • Cleaning more time consuming • Holes in mesh can block increasing treatment time • Poor breathing technique can increase treatment time • Slower than I-neb ®

Cleaning and disinfection of the nebuliser devices is vitally important (follow manufacturer's advice).

In-Patients: All children admitted will be assessed and physiotherapy requirements established. Treatment is also continued over the weekend as appropriate. If necessary, devices such as the Vest, Cough Assist, Intermittent Positive Pressure Breathing (IPPB), Non Invasive Positive Pressure ventilation (NIPPV) or ultrasonic nebulisation can be used. Children will also be seen pre- and post-general anaesthesia to ensure they can clear sputum effectively. An exercise test may also be performed where indicated. Prior to discharge, the home regimen will be reviewed; as well as exercise and progression of treatment where appropriate. Liaison with homecare physiotherapy service occurs as required.

6.15 Oxygen

All children with CF admitted with a respiratory exacerbation should have a ***continuous*** overnight oxygen saturation performed on the first or second night (especially if FEV_1 <50% or resting SpO_2<92%). The minimum is that every child admitted must have a spot SpO_2 on admission and during the first night. Oxygen therapy is usually given in hospital if saturations are <90% for >5% of the time, but this is not evidence-based. Oxygen, method of delivery and target saturations must be prescribed on the relevant section of the drug chart (Doctors) and changes to the flow rates documented in the relevant section by nursing staff.

If saturations were low and oxygen was required at the start of the admission then the overnight monitoring should be repeated at the end of the admission. If they remain low (**saturations <90% for >5% of the time**), then consideration should be given to providing oxygen at home, almost always only at night. When home oxygen is initiated, an overnight transcutaneous CO_2 should also be recorded, as it can rise slightly when oxygen therapy is initiated.

As this is for >8 hours then an oxygen concentrator is preferred to cylinders. The whole process is handled by the occupational therapy (OT) department. A Home Oxygen Order Form (HOOF) needs to be faxed to the relevant oxygen company, depending on the child's GP's address. Clear instructions for prescribing oxygen are available on www.bprs.co.uk/oxygen.html.

When ordering home oxygen, please also contact Andrew Montgomery in OT (ext 4453, bleep 7755), who will help facilitate the process.

6.16 Non-Invasive Positive Pressure Ventilation (NIPPV)

NIPPV has a number of uses:

- Nocturnal or daytime use of NIPPV is helpful in those with very advanced disease especially with CO_2 retention, and also patients requiring a 'bridge to transplantation'. It improves sputum clearance, reduces the work of breathing, may stabilise lung function and improve exercise capacity. Its requirement in children is most uncommon and needs prior sleep studies and careful evaluation.

- Occasionally, nocturnal NIPPV may be used during an in-patient exacerbation to improve sputum clearance in particularly those who are very tight and obstructed. A 2009 Cochrane review demonstrated few studies but some benefits especially in dyspnoea

- More commonly, the BIRD inspiratory positive pressure device can be used as an adjunct to chest physiotherapy for an inpatient – the principle being that positive pressure gets air 'behind the sputum', aiding its clearance and supporting the patient's work of breathing. Recently an NIPPV device (e.g. the iSleep) is being trialled on patients at home who normally do well with the BIRD as an inpatient. Nevertheless care should be taken with new technology as the Hayek negative pressure vibrating chest device has objectively not been found to improve sputum clearance.

7. Gastrointestinal & nutritional care

7.1 Nutritional care & oral calorie supplements

The aim of nutrition intervention is to promote normal growth and development throughout life. Although patients with CF can have widely varying energy requirements, an intake of 120% to 150% of the Estimated Average Requirement (EAR) for energy is considered suitable for most patients.

Many children eat well and are able to meet their nutritional requirements with regular meals and snacks; however poor appetite (and the resulting poor intake) is sometimes a challenge. This may be a consequence of a variety of factors, including poor lung function or recurrent exacerbations, excessive cough, untreated gastro-oesophageal reflux, depression, gastrointestinal disturbances (i.e. constipation, DIOS, abdominal distension or pain), or a dislike of high-energy foods.

Nutritional care plans are individually tailored and include practical suggestions on how to increase energy intake and meet nutritional requirements. This may include food fortification advice (such as the addition of butter/margarine/oil/cream to foods to increase the caloric density of the food), or use of prescribed oral supplements.

Promoting a high-fat, high-energy diet should be coupled with encouraging a balanced and varied diet, where possible including modified family foods. This will help to avoid behavioural feeding difficulties at a later stage. Previously, foods of low micro-nutrient value, such as sweets and sugary drinks, have been promoted, although we now try to encourage more nutrient rich, yet still high calorie snacks.

A dietitian is available in CF clinic and reviews all children on a regular basis, although not necessarily at each appointment. Each review will assess growth, calorie intake, enzyme dosage and provide education as needed. All children must be weighed (**in underwear only**) and measured at every clinic visit. In addition infants under 1 year should have their head circumference measured. This data should then be plotted on appropriate weight, height and BMI percentile charts.

Criteria for different stages of nutritional intervention

	<5 years	5-18 years	> 18 years
Normal nutritional state- *Preventative counselling*	Wt/ht 90-110%	Wt/ht 90-110%	BMI 19-25 kg/m^2 and/or no recent weight loss
Consider supplements	Wt/ht 85-89% or weight loss over 4 months or plateau in weight over 6 months	Wt/ht 85-89% or weight loss over 6 months or plateau in weight over 6 months	BMI <19 kg/m^{2}or 5% weight loss over more than 2 months
Aggressive nutritional support	Supplements tried and either wt/ht <85% or weight falling 2 centile positions	Supplements tried and either- wt/ht <85% or weight falling 2 centile positions	Supplements tried and either- BMI <19 kg/m^2 or >5% weight loss over more than 2 months

For all age categories pay special attention if stunting is evident, defined as ht/age of <90% or height centile <0.4th (UK Cystic Fibrosis Trust Nutrition Working Group, April 2002).

If dietetic counselling fails to improve nutritional status then prescribable dietary supplements should be considered. These are available in a variety of different flavours and presentations, an outline of which is given below:

Milk Based Supplements	Infant (Birth to 18 months)	• SMA High Energy (Wyeth) • Infatrini (Nutricia) • Similac (Abbott) • Concentrated Standard feed – *must* be supervised by the dietitian
	Paediatric	• Paediasure Plus (Abbott) • Fortini (Nutricia) • Frebini Energy (Fresenius Kabi)
	Adult (1.5-2.6 kcal/ml)	• Build-up (Nestle) • Ensure Plus (Abbott) - Also available in yoghurt style flavour • Scandishake (Nutricia) • Calshake (Fresenius Kabi) • Enshake (Abbott) • Fortisip and Fortisip Compact (Nutricia) • Fresubin Energy (Fresenius Kabi) • Clinutren 1.5 (Nestle)
Juice Based Supplements	Paediatric	• Paediasure Plus Juice (Abbott) **
	Adult (1.5 kcal/ml)	• Fortijuice (Nutricia) ** • Provide Xtra (Fresenius Kabi) ** • Clinutren Fruit (Nestle) **
Powder and liquid polymers to add to foods	Carbohydrate:	• Maxijul (SHS) ** • Polycal (Nutricia) ** • Polycose (Abbott) ** • Caloreen (Nestle) **
	Fat emulsions:	• Calogen (SHS) • Liquigen – MCT fat source (SHS)**
	Carbohydrate + fat mixtures:	• Duocal (SHS) • Procal and Procal 'Shot' (Vitaflo)

** DO NOT NEED ENZYMES

Generally no more than 20% of the EAR should be provided by dietary supplements except during cases of acute infection or if the patient is being considered for enteral feeding. Excessive consumption may impair appetite and decrease nutrient intake from normal foods. Supplements should be given apart from meal times or at bedtime. Parents can use supplements creatively (e.g. in cooking) to encourage intake and avoid taste fatigue

Children with unexplained failure to thrive should always have urinary & serum electrolytes checked. A spot urine sodium of <20 mmol/L indicates a low total body sodium, and requires correcting in order for weight gain to occur. A borderline low serum potassium almost certainly means a low total body potassium. CF-related diabetes and gastrointestinal causes (such as lactose intolerance or coeliac disease) must be excluded, and allergy should also be ruled out if suspected. See Section 7.3 for a full list of investigations to consider in older children with poor weight gain.

Fat-soluble vitamins (A, D, E and K) are needed for those with pancreatic insufficiency. For details on appropriate supplements see Section 11.2b.

7.2 Pancreatic enzyme replacement therapy (PERT)

Approximately 90% of CF patients in northern Europe are pancreatic insufficient. The most effective test to confirm the diagnosis is to measure **faecal elastase**, which is low in people with pancreatic insufficiency. This is not affected if the children are already taking pancreatic enzymes. The sample should be sent to Biochemistry who will have it assayed in the Virology Department of Sandwell and West Birmingham City Hospital.

Normal	>200 mcg/g stool
Mild/moderate pancreatic insufficiency	100-200 mcg/g stool
Severe pancreatic insufficiency	<100 mcg/g stool
CF pancreatic insufficiency (typically)	<15 mcg/g stool

Levels of <15 mcg/g stool are usually seen in CF patients who are pancreatic insufficient. Normal faecal elastase levels are expected by day 3 in term infants and by 2 weeks of age in those born at less than 28 weeks gestation, so tests should not be performed before this time. Due to the delay in receiving test results for faecal elastase, requesting faecal fat globules by microscopy may be a useful test as an easier indicator for the need to commence pancreatic enzyme therapy.

Whilst some infants may initially be pancreatic sufficient, they may become insufficient over time. 90% of children with CF are likely to exhibit pancreatic insufficiency by 12 months of age. As pancreatic sufficient (PS) children can become insufficient when older, this must be considered should they present with symptoms of fat malabsorption or poor weight gain.

Requirement of PERT varies widely and should be assessed on an individual basis following dietary or symptom analysis. Abdominal symptoms and stool characteristics such as oily, floating, grey or yellow loose stools are indicators that PERT is not optimal. Performing a test for faecal fat globules may be useful if symptoms are present or a child is demonstrating faltering growth. A three-day faecal fat collection is occasionally carried out (doctor request). Biochemistry provides a sample pot (please call Portering to arrange for a pot to be delivered) and instructions for completing the test are provided by the dietitian who will then analyse a 3-day food record and correlate this to enzyme intake and faecal fat excretion.

Pancreatic enzymes should be taken with all meals, snacks and drinks containing fat. Education on the amount of Creon taken with different foods is provided by the dietitian. Some foods do not require enzyme supplementation. They include:

- Fruit (except avocado) and vegetables (except potatoes)
- Sugar, jam, honey, and syrup
- Fruit juice, fizzy drinks, and squash
- Sorbet or fruit lollies
- Jelly and boiled sweets
- Juice-based supplements

Enzyme capsules should be swallowed whole at the start of a meal. Ideally meals should be finished within 20-30 minutes; however this is not practical for all children so additional

enzymes may be given towards the end of a meal or between the main course and the pudding. It is important to have quick and easy access to enzymes to aid compliance. Between the ages of 2-5 years old children should be encouraged to learn to swallow capsules whole. Capsules can still be opened out and taken with water, fruit puree or yoghurt but this may compromise their effectiveness, and can be less convenient, especially as a child get older.

Enteric-coated microspheres should be used even in young babies (Creon Micro, Solvay). Babies below 4 months of age should have the PERT granules from a spoon in a small amount of apple puree (enough to suspend the granules in) at the start of feeding. From 4 months fromage frais can be used if preferred. Enzyme granules ***must not*** be mixed into a bottle formula or into a meal (especially hot food) as the enzymes will be activated before they reach the small intestine. In addition, enzyme granules are unpleasant to chew, can cause ulceration of the mouth and gums, and can deter children from eating.

Creon Micro may be put down a feeding tube, but must be well flushed to avoid blocking and degradation of the tube itself. Only tubes of FR 12 are suitable as granules will not pass easily through a smaller tube, in which case Pancrex powder will be used.

Although there are no specific dosing guidelines for enzymes, starting dose tends to be:

- Babies: ½ -1 scoop of Creon micro granules per 120ml feed (1 scoop per 4g fat)
- Toddlers: 2 Creon Capsules with meals, 1 with snacks
- Pre-school: 2-3 Creon with meals, 1-2 with snacks
- School age: 4-6 Creon with meals, 2-3 with snacks
- Adolescents: 5-8 Creon with meals, 2-3 with snacks

The majority of our patients use the Creon 10,000 preparation. Higher strength enzymes are available but are not usually used in children. Excessive enzyme dosing can also lead a sore bottom and hyperuricosuria, so a dose exceeding 10,000 IU lipase per kg is not usually recommended. If excessively high doses appear necessary, enzyme efficacy can be improved by using a proton pump inhibitor or H_2 antagonist to reduce gastric acid output.

Barrier nappy cream is useful in babies with a sore perianal area to prevent excoriation.

Psychology referral may be useful for help with learning to swallow creon capsules whole, in older children.

Note
Many specialist infant feeds will still require enzymes: Neocate (SHS), Nutramigen (Mead Johnson), Pepti (Aptimil). The following feeds also likely to still need enzymes but given in smaller doses than usual: Pregestimil (Mead Johnson) and Pepti-Junior (Cow and Gate).

7.3 Supplementary enteral feeding & gastrostomy

Supplemental feeds provide long term “aggressive” nutritional support. Enteral feeding via a gastrostomy or occasionally a nasogastric (NG) tube is considered when there has been unsatisfactory weight gain with progressive fall on the centile chart in spite of the following:

- Repeated attempts to improve dietary intake including appropriate dietary modification and trials of various high-energy nutritional supplements

- Control of malabsorption (consider causes other than pancreatic exocrine deficiency)
- Co-operation with treatment
- Optimal control of respiratory disease
- Involvement of clinical psychologist and of course dietitian
- Exclusion of other conditions, especially diabetes mellitus and Pseudo-Bartter's syndrome.

The following investigations should be carried out:

- Oral glucose tolerance test or CGMS
- Urinary sodium
- Serum electrolytes
- Coeliac screen: anti-gliadin IgG & IgA; also TTG (anti tissue transglutaminse) IgG & IgA. Ensure that the total serum IgG/IgA is known as well
- ESR

We have found that the need for gastrostomies has fallen over the last decade.

Gastrostomy feeds are usually given as a continuous infusion (by feeding pump) for 8-10 hours overnight, with a 1-2 hour break before physiotherapy in the morning. Oral intake is encouraged during the day. Occasionally addition feeds are used to supplement daytime intake, particularly during acute illness. Allowing teenagers a night off each week can help with compliance. Around 40-50% of the EAR should be given via the tube, then weight and height should be reviewed regularly.

Caution should be used before placing a gastrostomy in a child with behavioural feeding difficulties. The team may wish to seek psychology input for the family and child, and recognise that gastrostomy placement may not be relied on to solve feeding issues.

Patients and parents should be carefully introduced to the concept of a gastrostomy and should be educated about the potential positive effects of a gastrostomy tube on growth, timely initiation of puberty, family stress levels, and overall health. Some children and parents find it useful to speak to a patient who already has a tube in place. Body image may be a problem, particularly in teenage girls who prefer to be “slim.” Early recognition of a distorted body image is essential, so that counselling can be arranged.

The gastrostomy tube is inserted endoscopically under a short general anaesthetic. The procedure is carried out at Chelsea & Westminster Hospital by a Consultant Paediatric Gastroenterologists (usually Dr John Fell) together with Mr Muntha Haddad or Mr Simon Clarke (Consultant Paediatric Surgeons) on a monthly Thursday afternoon list. Repairs and replacements may sometimes be carried out on the weekly Thursday afternoon list.

To **organise** a gastrostomy, please contact Dr Fell’s secretary on 0208-746 8000 ex 58628. Our dietitian and CF Nurse Specialist must also be aware of the arrangements as the setting up of home enteral feeds usually takes at least 5 days. Concomitant gastro-oesophageal reflux must be checked for by pH study; a Nissen’s fundoplication may be necessary as a gastrostomy can worsen reflux. The child is admitted to Chelsea & Westminster Hospital; see section 10.1 for peri-operative antibiotic regimen. Occasionally a child will need 7-10 days of IV antibiotics pre-PEG insertion, which is provided at the Royal Brompton Hospital or the local hospital. The child is then transferred as a day case to Chelsea & Westminster Hospital

for gastrostomy insertion. Feeds may be initiated 24 hours after insertion, and after the PEG has been primed with Dioralyte to ensure that there is no leakage from the PEG site.

For problem solving with gastrostomies first refer to the link nurse on Rose Ward and if they cannot solve the problem please contact the Paediatric Gastroenterology Nurse at Chelsea & Westminster Hospital on 0208 746 8627 or 0208 746 8000 Bleep 4988
Email: grant.mallon@chelwest.nhs.uk.

Types of tubes

Percutaneous endoscopic gastrostomy (PEG)

- *Corpak 12 FR*
  - This is the type used at Brompton and Chelsea & Westminster Hospitals.
  - Used if a change to a button-type PEG is intended (this is done 3 months post PEG insertion).
  - Large and unwieldy (therefore not a good choice for a permanent PEG).

- *Fresenius 9-12 FR*
  - Cosmetically acceptable, but the stoma closes easily if the PEG falls out.
  - Must be turned daily.
  - Change under GA only.
  - In theory should be changed every 12-18 months (in practice lasts 2-3 years).
  - We do not use this type.

Button gastrostomy

- *Mini or Mic-Key* Buttons
  - Cosmetically preferable
  - May leak if not well fitted
  - Must be turned daily; water balloon must be re-inflated weekly
  - Can be changed in clinic or by a community nurse, usually every 3-6 months
  - Can sometimes be placed as initial device with the fastener method - requires referral to the Paediatric Surgical team at Chelsea and Westminster Hospital.

PEG tube care-

- Clean around the exit site of the stoma daily using water and a soft cloth. It is important that the area is dried gently but thoroughly.
- Gently rotate the tube 360 degrees daily.
- Tape the tube to the abdomen.
- For the first 3 weeks you should not fully immerse the stoma in water so a shower or very shallow bath is best.
- Check the area around the tube for redness, inflammation, swelling, irritation, skin breakdown, soreness or excessive movement of the tube. If you are concerned about any of these or there is a temperature or smelly discharge present please contact the hospital.
- Change the position of the clamp on the tube regularly.
- Flush the tube before and after all feeds and medications with at least 10mls of water.
- Ensure all medications are in liquid form.
- Maintain oral hygiene with regular teeth brushing.

Types of feed

Most children with CF and who are pancreatic insufficient will gain weight well if given a standard high energy feed. The dietitian can advise on appropriate enzyme doses to give with this feed. Patients are usually advised to take half to two-thirds of the enzyme dose pre-feed and the remainder post-feed. Waking children during the night to provide enzymes while a feed is running is strongly discouraged.

If there continues to be ongoing issues with malabsorption and poor weight gain, then an elemental feed of hydrolysed protein and a fat source from medium chain triglycerides (MCT) may be considered. Because of the nature of these feeds most will not require enzymes with them, or they will require a lower dose.

Most feeds are pre-constituted 'ready to hang' bottles and come in a closed system. These feeds are easy to use at home and reduce the risk of microbial infection. Powdered feeds such as Emsogen need to be made up with water; they can be inconvenient but are more flexible when it comes to adjusting the calorie content of the feed. Each child is individually assessed and the best feed and regime is chosen to match his or her nutritional, social and lifestyle needs.

A summary of possible enteral feeds is given below (other feeds are available and are occasionally used). Also indicated is whether enzymes are required, or needed at a reduced amount. Fibre containing feeds are not included as they are not often used in CF patients.

	Feed Name	Enzymes			Comments
		Yes	No	Reduced dose	
Infant feeds (Birth – 12 months/8kg)	Expressed Breast milk (Follow RBH guidelines on storage and use)	✓			0.67 kcal/ml (Can be fortified under dietitian supervision)
	Standard Infant formula	✓			0.67 kcal/ml
	Neocate (SHS)	✓			0.71 kcal/ml
	Pepti- Junior (Cow and Gate)			✓	0.66 kcal/ml
	SMA High Energy (Wyeth)	✓			0.91 kcal/ml
	Infatrini (Nutricia) / Similac (Abbott)	✓			1.0 kcal/ml
Paediatric Feeds (8-20 kg or >1 yr of age)	Paediasure Plus (Abbott)	✓			1.5 kcal/ml
	Nutrini Energy (Nutricia)	✓			1.5 kcal/ml
	Frebini Energy (Fresenius Kabi)	✓			1.5 kcal/ml
	Peptamen Junior (Nestle)			✓	1.0 kcal/ml (Can be made-up more concentrated)
	Pepdite MCT 1+ (SHS)		✓		0.91 kcal/ml (Can be made-up more concentrated)
	Nutrini Perpisorb			✓	1.0 kcal/ml
Adolescents feeds	Tentrini Energy	✓			1.5 kcal/ml (7-12 years / 21-45 kg)
Adult feeds (>20kg)	Osmolite 1.5 (Abbott)	✓			1.5 kcal/ml
	Ensure TwoCal (2 kcal/ml) (Abbott)	✓			2 kcal/ml
	Nutrison Energy (Nutricia)	✓			1.5 kcal/ml
	Fresubin Energy (Fresenius Kabi)	✓			1.5 kcal/ml
	Peptamen (Nestle)			✓	1.0 kcal/ml
	Emsogen (SHS)		✓		0.88 kcal/ml (Can be made-up more concentrated)

The dietitian will educate the family about the feed preparation and administration, and work with the Community Team and enteral feeding companies to provide equipment and training for parents and caregivers. Home enteral feeding companies loan feed pumps to the patient at home (as most patients receive their feeds overnight via a feeding pump), and will also deliver feeds directly to the patient. Ancillaries (e.g. giving sets, feed reservoirs) are usually funded from the Local Health Authority and the dietitian will make arrangements for these to be supplied at home.

7.4 Management of feeding difficulties

Feeding difficulties are common in CF and can present a significant challenge for families and CF professionals. It is important for CF children and their parents to develop a good relationship with food and nutrition despite the strong emphasis on weight and growth.

Feeding difficulties can consist of a combination of difficult child behaviours (e.g. food refusal, fussy eaters) and inappropriate parental responses (e.g. force-feeding, shouting or making multiple meals if the family meal is refused).

Parents who are concerned about their child's feeding behaviour or who would like some suggestions to minimise stress at mealtimes can contact the clinical psychologist or dietitian directly or ask to be referred by a member of the team. A referral for feeding difficulties can also be made by a professional with the family's agreement. It is helpful to refer feeding difficulties earlier rather than later, before more complex behaviour patterns have become established over time.

For most parents weaning infants onto solid food is an enjoyable experience; however they will usually require extra help and advice at this stage. The Department of Health guidelines regarding types and textures of foods when weaning are appropriate for children with CF. The dietitian should be available at this time to offer individualised advice to ensure that PERT doses are judged correctly depending on what foods are offered.

The following principles are encouraged to reduce the risk of developing behavioural feeding problems:

- Having a consistent approach from all adults involved with feeding a child.
- Creating a relaxed and enjoyable feeding environment, avoiding distractions such as the television.
- Making food as attractive as possible.
- Giving gentle encouragement to eat and providing positive feedback and praise for good behaviour (as opposed to focussing on the child when behaviour is bad).
- A structured meal and snack time pattern appropriate to the child's age and lifestyle.
- Limiting mealtimes to around 30 minutes. Meals that last longer than this rarely result in higher calorie consumption.
- Not offering alternative meals or snacks (especially biscuits or crisps) if the first meal is refused.
- Engaging children in feeding activity (for example messy food play, self feeding and simple food preparation).
- Where possible dining with family or peers.

7.5 DIOS and constipation

Distal Intestinal Obstructive Syndrome (DIOS) is a common complication in CF. The incidence varies widely but it only affects those with pancreatic insufficiency. The pathophysiology is not fully understood, but there are often multiple contributory factors including:

- Dehydration
- Rapid increase in enzyme dosage
- 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 right lower quadrant, abdominal fullness and a palpable mass in the right iliac fossa. The children often report having their bowels open as usual, or sometimes diarrhoea (from overflow).

Differential diagnosis

Constipation, appendicitis, intussusception, volvulus, adhesions post abdominal surgery, fibrosing colonopathy, biliary tract or gallbladder disease, acute pancreatitis, urinary tract infection.

Investigations

A plain abdominal x-ray (AXR) is usually all that is necessary to diagnose DIOS or constipation.

However if there if 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 /gastrografin 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.
- Ensure patient has well established toilet routine (try to go after meals), even at school.

- Laxatives may help e.g. lactulose 5-20 mls bd or movicol.
- If ongoing malabsorption is documented consider:-
  - Acid reduction with ranitidine (very bitter in liquid form) <6 months 1-3mg/kg TDS; > 6 months 2-4mg/kg bd (max dose 300mg bd)
    or omeprazole 0.4-0.7 mg/kg bd initially, (maximum dose 40 mg/day. To exceed this dose i.e. up to 1.5 mg/kg bd is a consultant decision).

If continuing problems refer to Dr John Fell, Consultant Gastroenterologist at Chelsea and Westminster Hospital.

2. Acute

- Gastrografin (oral) 25 mls (<15kg) in 75 ml water or juice
  50 mls (15-25kg) in 150 ml water or juice
  100 mls (>25kg) in 200 ml water or juice
  - Patient must be **well hydrated** before, during and 3 hours post gastrografin, as it is highly osmotic. The suggested fluids above are the minimum. Be particularly careful in babies & infants who can easily become dehydrated. This is often done as an in-patient, especially in the more severe cases. IV fluids may be required.
  - Repeat at 24 hours if no response but not if symptoms worsen.
  - Follow up with oral lactulose for 1 week and review chronic management above.
  - Contraindicated if complete bowel obstruction.

- Rectal gastrografin- consider if oral administration has failed or if there is vomiting due to obstruction. This is rarely used and is a last resort. Administer under radiological guidance only. Watch for dehydration and perform a plain AXR at 1 hour to exclude massive dilation. If the latter is present, urgent referral to a paediatric surgeon is required.

- Oral acetylcysteine- tastes like rotten eggs. The 200mg/ml injection can be given orally and should be mixed with water, orange juice, blackcurrant juice or coke to a concentration of 50mg/ml. Alternatively 600mg tablets are available.

1month – 2 years	0.4 - 3g STAT
2 – 7 year	2 – 3g STAT
>7 years	4 – 6g STAT

- Klean Prep (see formulary section 11.2e).
  - Admit patient.
  - 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).
  - Start regular lactulose and review chronic management.

Constipation

If severe should be considered as part of DIOS spectrum. However beware increasing enzyme doses when all that is needed is simple constipation treatment. Main differential from DIOS is that constipation tends to be limited to rectum.

Treatment:

- Ensure adequate fluid intake.

- Lactulose 5-20 mls twice daily (see formulary 11.2f)
  or Movicol may be used (see formulary 11.2f).

7.6 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 later childhood.

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. Guidance from Kings is that in the absence of hepato- or splenomegaly, and with normal liver function, they would not start ursodeoxycholic acid but would repeat the ultrasound in 1 year.

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.
- Routine annual assessment ultrasound on alternate years from aged 5 years and above.
- 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 children with hepatomegaly, significantly elevated liver function tests, abnormal clotting or evidence of cirrhotic changes on liver USS:

- Ursodeoxycholic acid (increases bile flow) – 10-15 mg/kg bd. 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. In cases of significant liver disease, 5-15 mg/kg tds may be used.
- Vitamin K (if prothrombin time prolonged) – If PTT corrects then continue with daily oral vitamin K (see section 11.2b). Occasionally 2 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 BNFc)
- Caution with itraconazole and voriconazole – See BNFc

Referral to hepatologist

- Refer patients with cirrhosis or evidence of portal hypertension.
- Also refer anyone with atypical abdominal pain or abdominal sepsis or sudden changes in liver function tests.

- We now use Dr Marianne Samyn at King's College Hospital for children with significant liver disease - 020 3299 5614 (or secretary 020 3299 1162).
- Prof David Westaby attends the adult Brompton CF clinic once a month, and patients who are about to transition to our adult team may be referred to him for continuity.

Treatment of complications - (All management of complications should be discussed with the child's hepatologist)

- Portal Hypertension
  - Splenomegaly - Avoid contact sports.

  - Varices (oesophageal and gastric) -

    - **Acute management**: Initial volume resuscitation with blood. Advice for further management should be from hepatology team but may include: intravenous octreotide, terlipressin (splanchnic vasoconstrictor), endoscopic sclerotherapy.

    - **Chronic management**: As directed by hepatologist: examples include endoscopic sclerotherapy, non-selective β-blockers (beware if child has airflow obstruction) or surgical shunts e.g. Transjugular intrahepatic portosystemic shunts.

  - Ascites – Standard treatment includes: sodium restriction and diuretics.
  - Hepatorenal syndrome - rare in CF.
  - Spontaneous bacterial peritonoitis - rare in CF.
  - Hepatic encephalopathy - rare in CF.
  - Hepatocellular failure is rare but ominous.

- Jaundice - uncommon. Exclude other causes (sepsis, drug reaction, and haemolysis).
- Gallstones - high prevalence but not always symptomatic in CF. Referral to surgeon if symptomatic for consideration of cholecystectomy.

7.7 Iron status

The quoted incidence of iron deficiency anaemia in CF patients varies markedly. Iron deficiency anaemia (hypochromic microcytic anaemia with low ferritin) is the extreme end of a spectrum of iron deficiency. The earliest features are low/deficient iron stores, i.e. low ferritin, which progresses to iron deficient erythropoiesis i.e. low ferritin, raised TIBC,

reduced transferring saturation and hypochromic red cells. This will progress to anaemia if the iron stores are not restored.

Many are cautious about supplemental iron in CF patients, especially those infected with *P aeruginosa*, as the organism requires iron for its growth and has developed iron scavenging mechanisms. It has also been shown that free iron i.e. that unbound to ferritin, catalyses the generation of highly reactive hydroxyl radicals and promotes oxidative cell injury. Increased concentrations of iron, ferritin and isoferritins have been found in the sputum of adults with stable CF.

Another important cause of hypochromic microcytic anaemia is anaemia of chronic disease, where iron is poorly utilised due to the increase in certain cytokines. Here the major differentiator from iron deficiency anaemia is a normal or raised ferritin. These patients would not benefit from oral iron supplementation.

It must also be remembered that ferritin is also an acute phase reactant and can go up in acute infection/inflammation (although this is rarely seen in practice).

Our policy is to treat overt iron deficient anaemia, rarely seen in our patients (1%), but we tend not to give iron at the earlier stages of reduced stores due to concerns over its potential adverse effects on lung disease. In addition it is often poorly tolerated with gastrointestinal side effects. When necessary, we use sodium feredetate (sytron liquid) or if not tolerated ferrous fumarate liquid, whilst in older children 1st line is ferrous sulphate tablets (see BNFc for dosage). Bloods should be checked after 3 months of treatment. For low iron stores we recommend increasing the iron content of the diet, in the form of red meat, green vegetables and eggs.

	Iron stores	**Transport iron / iron supply**			**Functional iron**	
	Serum ferritin	Serum TIBC	Serum transferrin saturation	Hypochromic red cells	Hb	MCV
Iron deficiency						
Storage depletion	↓	N	N	N	N	N
Iron deficient erythropoiesis	↓	↑	↓	↑	N	N
Iron deficiency anaemia	↓	↑	↓	↑	↓	↓
Iron malutilisation						
Anaemia of chronic disease	N or ↑	↓	↓	N or ↑	↓	N or ↓

8. Other non-pulmonary complications of CF

8.1 Cystic Fibrosis-Related Diabetes

Contacts

Consultant Paediatric Endocrinologists, Chelsea & Westminster Hospital
Dr Nicola Bridges
Dr Saji Alexander

Diabetes Nurse Specialist, Chelsea & Westminster Hospital
Ms Karen Spowart

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. CF related diabetes (CFRD) is rare in those under 10 years although up to a third of this age group will already have impaired glucose tolerance. 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

"We are now obsessed with CFRD".
CFRD reduces life expectancy so is critically important. 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.

Screening for abnormal glucose tolerance and diabetes in CF

"The more you look, the more you find".

When to test for glucose status in CF:

- Current CF Trust recommendation is for OGTT once yearly in all CF patients over 12 years; this has not been fully implemented in many units because of the limitations of OGTT as a guide to management.
- Clinical concerns- poor weight gain, decline in lung function with no other obvious cause.
- 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 HbAic 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.

Available tests of glucose status in CF

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. OGTT can be used as a quick screening test.

CGMS

A subcutaneous sensor gives a profile of glucose levels for up to 6 days (we use for 3 days normally). The plastic sensor reads glucose in the interstitial fluid every 5 minutes. The sensor needs to be calibrated with blood glucose measurements twice daily for as long as 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.

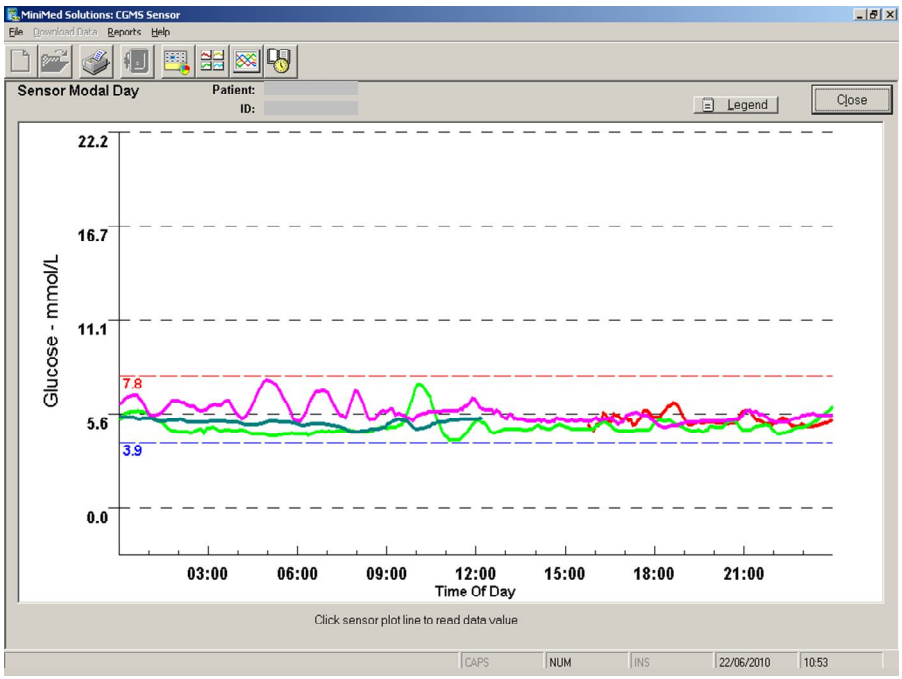
Disadvantages -

- 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).

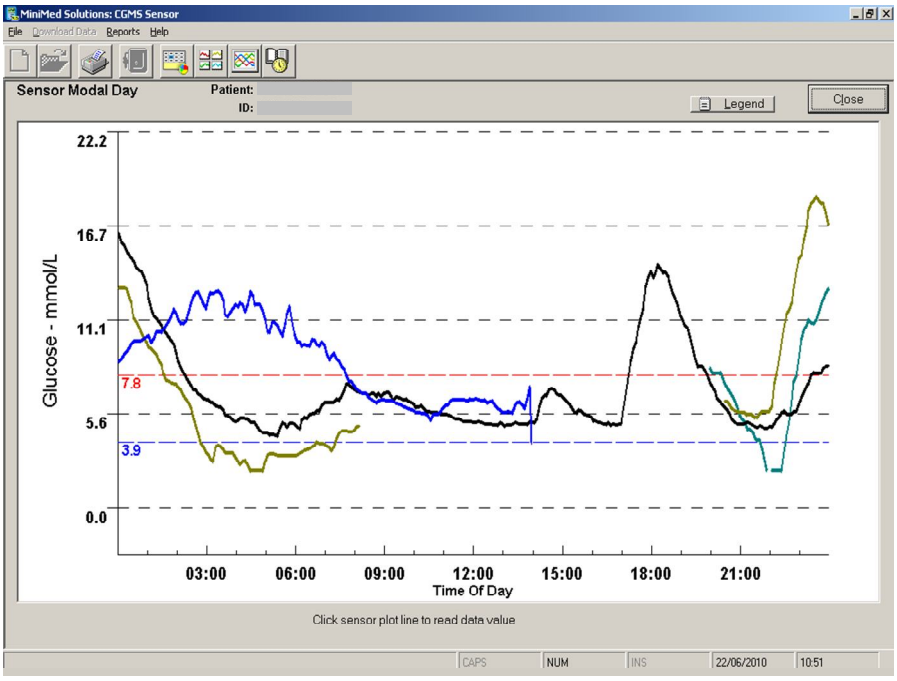
When to use -

- 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).
- CGMS may give less useful information if the glucose levels are already known to be very high, and is not a good way of documenting hypoglycaemia

Normal CGMS trace



Abnormal CGMS trace



Oral glucose tolerance test

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 <7.0mmol/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

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

- *Preparation*
  In the standard test, the child is fasted from midnight although drinks of water are allowed. SEE BELOW AS OUR 1ST LINE IS A NON-FASTING OGTT

- *Dose of glucose*
  1.75 g/kg glucose to a maximum of 75 g, as glucose monohydrate diluted in water (200-300 mls).

  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 blood for glucose at 0 mins (fasting) and give the glucose drink.
  Take blood for glucose at 120 minutes.
  Do not use fingerpricks unless in a needle phobic child.

Non fasted glucose challenge- our 1st line test.

The same guideline as above but not fasted, has been studied as another way to define glucose tolerance in CF. There are some practical advantages for outpatients. There may be a higher pickup of glucose abnormalities using this method of testing. While the results of this test do not define glucose tolerance status in the same way as a classical OGTT abnormal glucose levels found during testing are still significant and can guide treatment.

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.
- If it is difficult to get CGMS or random glucoses.
- OGTT is not needed if the diagnosis of diabetes is already established with CGMS or random glucose levels.

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.

When to use –

- If CGMS is not practical, or as an outpatient screen for glucose status.

HbA1c

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

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 NEVER 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. 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 adolescents 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

Adjusting insulin –

- 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.

Dietary advice

The family should have input from the dietitian at RBH. It is important that they understand that the dietary management is not the same as in other forms of diabetes and they do not need to adopt a “diabetic” diet. Families should be discouraged from reducing calorie intake to avoid starting insulin treatment.

- Calorie intake In CFRD maintaining adequate nutrition remains the priority and a high calorie and high fat diet must continue. Older children should avoid high sugar snacks and drinks between meals (i.e. regular fizzy drinks, juices and squashes, jellied sweets etc.) and substitute no-sugar-added drinks (i.e. diet fizzy drinks and squashes).
- Regular eating. Encourage regular meals and snacks (including breakfast if possible) because this makes the diabetes easier to control and improves weight gain. Food intake should not be reduced to try to control glucose levels; meals and snacks must be given whatever the blood glucose.

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

Hypoglycaemia

Hypoglycaemia is a blood glucose less than 4.0 mmol/L and any glucose lower than this should be treated even if the child feels well.
Symptoms of hypoglycaemia include confusion, irritability, pallor, fatigue, dizziness, and a "wobbly" or "funny" feeling, and many children can easily identify if they are low blood glucose.

Caregivers and schools should be given information about hypoglycaemia (e.g. the JDRF or Diabetes UK schools leaflet). 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: Give a rapidly-absorbed carbohydrate followed by a complex-carbohydrate snack. There is an understandable tendency to overtreat 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.

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 children 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 or Saji Alexander comes to the CF clinic on the 3rd Friday afternoon of each month. If possible arrange follow up in this clinic.

Chelsea and Westminster Hospital
There is a diabetes clinic every Tuesday morning and an adolescent clinic on the 4th Friday afternoon of each month, and patients can be reviewed here. If you want an urgent appointment please phone or e mail.

Some patients will have diabetes follow up arranged in their local hospital. Obviously it is important that all of the local team are aware of the management of CFRD. Nicola Bridges or Saji Alexander are always happy to discuss these patients and ideally we should review them at the Brompton as well. We give families our contact details and they can phone or e mail with problems.

Transition clinic
There is a regular diabetes clinic in adult outpatients at the Royal Brompton with Dr Kevin Shotliff and Nicola Bridges. Follow up in this clinic is discussed and arranged when they attend their transition appointment.

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 not at increased risk of thyroid disease or coeliac disease (compared to a CF child without CFRD) so this is not screened for, but regular eye screening and checks for urine albumin should be started in everyone over 12 years.

If a child with diabetes is admitted to the ward

- Please call Nicola Bridges or Saji Alexander to review the patient, even if things appear to be going well.
- Insulin injection and blood testing must be supervised. Make sure injection technique is good, they are rotating sites and that the correct dose is actually going in.
- Encourage good habits- blood testing at appropriate times, eating snacks and meals on time and not omitting insulin.
- Be very clear when prescribing insulin. Remember to be clear about time- better to write “before breakfast” than a time if that is what you mean. Never abbreviate units to u or IU because this can be misread as 0 or 10 and generate serious errors.
- Make sure you have the right equipment- the right strips for the meter, the right pen for the cartridges.

Surgery

Prior to any general anaesthetic a plan must be made to reduce the insulin while the child is fasting. Make sure anaesthetists are informed in advance.

Diabetic ketoacidosis (DKA)

DKA is rare in CFRD but it can still happen. DKA should be managed according to national consensus guidelines (these can be found on the BSPED website: http://www.bsped.org.uk/).

Other practical aspects

The school may need information. A plan needs to be made if blood testing or injections are occurring during school. Lunchtime doses of insulin can easily be forgotten and so an arrangement for a member of school staff to supervise and support is usually helpful. Legally, schools must provide support for children with medical needs. It is usually possible for school staff to check glucoses or give insulin but this would require training and a clear plan.

If a child 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.

Useful links

The CF Trust guidance –
http://www.cftrust.org.uk/scope/documentlibrary/Publications/diabetes.pdf

Other diabetes websites:

The Juvenile diabetes research foundation (JDRF) - www.jdrf.org.uk
The Diabetes UK website - www.diabetes.org.uk

The information is not all relevant to CF. The school information leaflet from the JDRF is very good.

8.2 Growth and puberty

8.2a. Growth

Average birth weight is slightly reduced in CF and growth rate (weight and length) is reduced (in **unscreened** babies) in the first year of life, mainly because of impaired nutrition. Once the diagnosis is made and nutrition is improved, catch up growth usually occurs. Height velocity in early childhood is normal although CF individuals are on average 0.5 SD shorter than unaffected children. In later childhood the height deficit increases. This is mainly due to delay in puberty, with worsening lung function and the onset of CF-related diabetes contributing. Adult height is usually within the normal range for the population but reduced compared to mid-parental height.

Pituitary function (growth hormone (GH), gonadotrophins, & ACTH) is normal in CF. Chronic infection, nutritional factors and steroid treatment result in GH resistance and can also reduce GH secretion. Gonadotrophin and sex steroid secretion is normal during puberty in CF but the changes tend to be delayed compared to the normal population. Boys reach normal testicular volumes in puberty despite the majority having azoospermia.

Patient monitoring

Height (measured with a stadiometer) and weight should be recorded at every clinic visit (minimum every 3 months) and plotted on the standard growth centile charts. In children under 1 year, head circumference (OFC) should be plotted. Assess the pubertal stages in older children and adolescents:

Girls Ask if pubic hair is present
Is there any breast development (part of chest examination)
Ask whether periods have started

Boys Ask if pubic hair is present
Has voice broken?

Who to be concerned about

The following groups may need further assessment or investigations:

- anyone whose relative position in terms of height or weight is falling (they are not maintaining their centile position).
- children who are very short (below 0.4th centile) even if they are maintaining their relative position.
- children who seem very short for their midparental height.
- delay of puberty. 98% of normal girls have started pubertal development (Tanner breast stage 2) by 13.7 years and 98% of boys have started development (testicular volume over 4 mls) by 14.2 years.

Assessment

Look for factors related to CF which may impact on growth:
- nutrition - intake or malabsorption
- chronic infection
- impaired glucose tolerance or CF related diabetes
- steroid treatment
- pubertal delay

Feeding behaviour problems are common in younger children and input from clinical psychologist may be valuable. Supplemental feeds should be started early (see section 7.3). Treatment can be offered for pubertal delay.

Consider checking for non CF related causes:
- coeliac disease
- hypothyroidism
- Turner syndrome (this is not always associated with clinical features and it is worth checking karyotype if a girl is very short).

Consider GH deficiency if there is continuing poor height velocity with no other explanation. Investigation requires stimulation testing and other causes should be excluded before this. There have been a number of studies of the use of GH in CF patients (without GH deficiency) which have demonstrated short term anabolic benefits, but there is no evidence for increased adult height.

Patients can be discussed with Dr Bridges or Dr Alexander at any stage. We are happy to look at growth charts or assess bone ages for patients.

Referral may be helpful for the following groups:

- Reduced height velocity or short stature, which does not seem to be caused by CF related problems.

- Children who are so short or growing so badly that they seem to be heading for a reduced adult height. An assessment of growth may be helpful even if the clinical issues underlying this are clear and cannot be altered.
- Concerns by family or child about height.
- Pubertal delay. Adolescents may not express their level of concern about this very clearly so consider referral even if they do not seem very bothered. There is significant delay if there are no signs of puberty by 14 years in a girl or 15 years in a boy, although referral can be made before then if there are concerns.
- High dose steroid treatment- there is little to offer in terms of treatment but an assessment of the situation can be helpful.

Bone age is a way of looking at how much growth there is still to come. There are ways of calculating adult height potential from bone age but they are not very accurate and likely to be overoptimistic in CF patients. Bone age is not likely to be helpful in children under 4 years. Assessment of bone age is operator dependent and results are more likely to be helpful if the score is assessed by someone with experience.

8.2b. Puberty

Pubertal delay is common in CF and is related to nutritional factors and infection. Pubertal development will occur eventually but can be very late in those with the most significant medical issues. Presentation may be with short stature or with concerns about development. There is no need to wait for an age limit before referring. Delayed puberty does not result in any benefit in terms of adult height. Delayed pubertal development has been found to contribute significantly to the psychological problems suffered by adolescents with CF.

Assessment of pubertal delay

- Height & weight.
- Tanner staging.
- Bone age if there are concerns about height.
- Gonadotrophin and sex steroid levels may be low even if the child is in already in puberty and are unhelpful.

Treatment of pubertal delay

Individuals with the most significant medical problems are the most likely to be delayed. Any nutritional problems should be addressed, and CF-related diabetes should be excluded as a contributory factor. Growth during puberty can be adversely affected by nutritional problems, infection and steroid treatment; all of which can reduce the increment in height achieved during this phase of growth. It may be appropriate to delay treatment if there is a realistic chance that medical status can be improved thus allowing growth without adverse effects. Often it is unlikely that any significant change will occur (and things might get worse), and it is then reasonable to go ahead with treatment to induce puberty even if optimum growth may not be achieved.

Potential benefits of treatment

- Psychological and social.
- Height.

- Bone density - Bone density reaches a peak during puberty as a result of sex steroid action. CF patients are at increased risk of low bone density and it makes sense to optimise it at this point.

Treatments available
Patients should be referred to Dr Bridges or Dr Alexander. Treatment to induce puberty mimics the gradual rise in sex steroids during normal puberty and aims to complete growth and development over about 2 years. Some individuals start to develop spontaneous puberty after a few months of treatment and medication can be stopped. There is no harm in stopping treatment at any point but if spontaneous puberty does not occur, it usually makes sense to take the individual to nearly adult height and development before stopping and reassessing endogenous function. Given in these doses treatment does not have an adverse effect on adult height.

Steroid treatment for induction of puberty

Females

Increasing doses of oral ethinyloestradiol:

- 2 or 2.5 micrograms ethinyloestradiol daily for 6 months (either 2 microgram tablets or one quarter of a 10 microgram tablet)
- 5 micrograms ethinyloestradiol daily for 6 month
- 10 micrograms ethinyloestradiol daily for 6 months
- 15 micrograms ethinyloestradiol daily for 6 months
- 20 micrograms ethinyloestradiol daily for 6 months

Adding in progesterone when 15 micrograms ethinyloestradiol is given or before this if there is any vaginal bleed, using -
levonorgestrel 30 micrograms daily or norethisterone 5mg daily for 7 days out of each 28 day cycle.

Males
Increasing doses of intramuscular depot testosterone esters as Sustanon (250mg in 1ml)

- 50 mg IM every 4-6 weeks for 6 months
- 100 mg IM every 4 weeks for 6 months
- 100 mg IM every 3 weeks for 6 months
- 100 mg IM every 2 weeks for 6 months

There are currently no reliable data to guide pubertal induction with topical sex steroids in males or females.

8.3 Bone Metabolism

A CF Trust guideline (2007 with an important addendum) is available and the link is:
www.cftrust.org.uk/aboutcf/publications/consensusdoc/Bone-Mineral-Booklet.pdf.

Increasing survival of CF adults has thrown up the finding of low bone density in at least one third of young adults. Clearly nutrition has a crucial role but latterly the impact of other

factors has become apparent. Recently it has been discovered that CFTR is expressed in bone, so bone disease may be a fundamental part of CF rather than a secondary consequence.

Investigation of bone mineralisation
Bone densitometry (DEXA scans) will be measured in patients at increased risk of developing osteoporosis, on alternate years, usually at annual review. Arrange via ext 8965. Interpretation of DEXA scanning in children and adolescents is complex. Because bones become bigger as the child grows, bone density measurements increase with age because there is more bone but this may not be due to more mineralisation. Bone density increases in puberty because of sex steroid action. There are normal ranges for children and adolescents - a child with delayed puberty will have a reduced bone density because the normal range compares with children with normally timed puberty. The trend between repeated measurements may be more helpful than comparing with the normal range.

An abnormal scan should be repeated in 6-12 months. A normal one should be repeated in 2 years. A repeat abnormal scan must be discussed with Dr Nicola Bridges (Chelsea and Westminster).

Risk factors for reduced bone mineral density

Steroids
Frequent courses of oral or intravenous steroids (particularly those with chronic ABPA) and those on high dose inhaled corticosteroids.

Calcium and Vitamin D
Ensure adequate calcium intake. Encourage intake of diary products and consider supplements in those who do not take them.

It is recommended that 25 hydroxy-vitamin D levels are measured annually. Because a large proportion of vitamin D comes from sunlight, levels are lower in winter and spring. Low vitamin D levels are very common in the general population (poor diet, pigmented skin and covering clothing are risk factors). Aim to maintain a serum 25 hydroxyvitamin D level over 75nmol/l to optimise bone health.

Normal levels 25 hydroxy vitamin D	> 75 nmol/L
Vitamin D insufficiency -	50 -75 nmol/L
Vitamin D deficiency -	25 -50 nmol/L
Severe Vitamin D deficiency -	< 25 nmol/L

Prophylaxis to prevent deficiency
400 IU of vitamin D daily should prevent deficiency in most individuals. This can be given as Vitamin A and D capsules (5000 IU of Vitamin A and 400 IU Vitamin D). Most ordinary multivitamin preparations contain 400 IU Vitamin D.

Treatment of vitamin D deficiency
Any one with a vitamin D level below 50nmol/l should be treated.
Give oral colecalciferol or ergocalciferol for 3 months:

- Infant 1 to 6 months: 3000 units daily
- Children 6 months to 12 years: 6000 units daily

- Over 12 years to adult: 6000 – 10000 units daily

This can be as colecalciferol or ergocalciferol liquid 3000 units/ml or as capsules available as 20,000units (given three times a week – Monday, Wednesday and Friday) or 50,000 unit capsules (given once a week).

10 mcg of colecalciferol or ergocalciferol is equivalent to 400 units.

In cases of severe deficiency, use IM preparation -

- Child 6 months-12 years: single dose of IM Calciferol 150,000 units
- Over 12 years: single dose of IM Calciferol 300,000 units

An alternative is intramuscular ergocalciferol as a one off dose (if compliance is likely to be poor or absorption uncertain). This will last 3 months:

- 6 months to 12 years- 150,000 units
- over 12 years- 300,000 units

Check 25 hydroxyvitamin D levels after 3 months, if > 75nmol/l and alkaline phosphatase normal, put child back on to prophylaxis. If not corrected, give another 3 months treatment.

Do not increase the dose of Vitamin A+D because there is a risk of Vitamin A toxicity. It is not possible to give sufficient vitamin D to treat deficiency as combined calcium and vitamin D preparations. Do not treat vitamin D deficiency with alfacalcidol.

Vitamin K

The role of vitamin K in osteoblastic activity has also become more apparent and indeed may be a prime factor in osteoporosis. Studies show vitamin K levels may to be low in CF patients, including those who are pancreatic sufficient. Vitamin K in multivitamin preparations is minimal and so we recommend oral water soluble vitamin K (menadiol) at a dose of 10mg/day in those able to swallow tablets and certainly over aged 8 years for both males and females. It is hoped this will lead to stronger bones in our adult patients.

Pubertal delay and hypogonadism

Sex steroids play a vital role in reaching adult bone density. Consider treatment with sex steroids if bone density is reduced in an adolescent with pubertal delay and assess whether adult levels of sex steroids have been achieved in post pubertal individuals.

Other clinical factors

Diabetes, reduced lung function (FEV_1<50% predicted) and immobility are risk factors for reduced bone density. Weight bearing exercise is of benefit and must be encouraged from an early age.

Bisphosphonate treatment

Bisphosphonate treatment should be considered after other factors have been addressed and usually only if there are fractures related to low bone density. There is little evidence as to long term effectiveness in CF. The drug binds permanently to the bone structure and for this reason there is concern about effects in the very long term. Bisphoshonates are rarely used and should be discussed on an individual basis in conjunction with Dr Bridges or Dr

Alexander. Bisphosphonate use is rarely associated with both osteonecrosis of the jaw and periodontal disease with a greater risk in those on steroids.

8.4 ENT complications

8.4a Nasal polyps

- Are uncommon in children but may occur in up to 40% of adults with CF.
- Uncommon < 5 years and onset is generally between 8-10 years.
- 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); see BNFc for dosages. Note though that growth failure has been reported with betamethasone nose drops.
- 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.

If conservative therapy is failing, refer to Mr Will Grant (who has a particular specialisation in nose problems), Consultant ENT surgeon Chelsea & Westminster Hospital (0208 746 8345). Mr Jonny Harcourt is present in Brompton clinic on the 2nd Friday of every month from 11am-12.40pm, and can see the children as well; simply book the patient directly into his clinic and send him a letter.

8.4b Sinusitis

- Although almost all children with CF have chronic paranasal sinusitis, only 1% are symptomatic.
- X-ray of the sinuses is of little value, as over 92% of all children 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 pneumatisation.
- 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).

- Long-term oral antibiotics may be of value (3-6 weeks), and we have found oral metronidazole may improve halitosis.
- Sinus washout is rarely successful, as the secretions are thick and tenacious; occasionally, more radical surgical drainage procedures are necessary to alleviate symptoms.

8.5 Arthropathy

Arthropathy may occur in up to 10% of children with CF and the mean age of 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, the children 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 of the children 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 (see section 6.11) re approval and funding). 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.

If there is doubt over diagnosis or management, refer to Dr Clarissa Pilkington (tel 0207 829 7887) at Great Ormond Street Hospital for Children.

8.6 Pseudo-Bartter's syndrome

An uncommon cause of metabolic alkalosis that has been seen as a presenting feature of CF as well as a complication in those with known disease. It is accompanied by chronic salt depletion and sometimes failure to thrive without severe dehydration. Principal findings are *hypokalaemic hypochloraemic metabolic alkalosis, sometimes with hyponatraemia.* This may be preceded by anorexia, nausea, vomiting, respiratory exacerbations, fever and weight loss.

Check venous sample in blood gas machine for bicarbonate. However after salt replacement, the metabolic abnormality resolves and weight gain follows rapidly. Treatment is with sodium and/or potassium chloride supplements, which may be required for many months.

Unexplained failure to thrive should always have urinary electrolytes checked, a spot urine Na^+ <20 mmol/l indicates low total body sodium that needs correcting. A serum potassium at the lower end of the normal range may still be associated with body depletion.

It is quite usual for a newborn screened infant under 3 months to have low urine Na levels. The normal range is less well defined so if they are thriving, we do **not** treat this with sodium supplements.

8.7 Fertility

Although it should be assumed that all males are infertile, this is not necessarily the case and so male contraception must be strongly encouraged, with the additional benefit of adhering to 'safe sex'. Condoms are mandatory! It is our duty to ensure that all boys are aware of this issue. The age of telling them may vary and occasionally is problematic if parents are reluctant for the issue to be discussed. We would encourage parents to tell their sons as early as possible, and we would wish to ensure they are informed by 8-12 years. The annual review is often a good time to do this. It is important to stress to them that infertility is not the same as impotence and that sexual performance is unaffected (although the volume of ejaculate is reduced). There are successful reports of CF men having children after microsurgical epididymal sperm aspiration and intracytoplasmic sperm injection (ICSI).

Girls are not infertile so again contraception must be encouraged. Useful information on types of contraception is available in a booklet entitled 'Cystic fibrosis and relationships' available via CF Trust website (see appendix XII). Care must be taken with oral contraception due to effect of short term courses of antibiotics, but long term ones (e.g. azithromycin) do not effect the Pill once the treatment is established (care again is necessary when they are started). Antibiotics for treating NTM, especially rifampicin can reduce the effectiveness of the Pill.

Female fertility may be reduced due to thickened cervical mucus and the issue of pregnancy and CF can be discussed with Mr Guy Thorpe-Beeston, Consultant Gynaecologist at Chelsea & Westminster Hospital (0208 746 8000). Generally women with CF need to be relatively healthy when planning a pregnancy.

8.8 Stress incontinence

Urinary incontinence is a condition where certain activities e.g coughing, laughing, jumping etc. leads to a leak of urine. This can be anything from a slight dribble to a complete emptying of the bladder. It is known that many women with CF are affected by urinary incontinence and it has become increasingly recognised that young girls may also be affected. This has been highlighted by the survey carried out at the Brompton, Great Ormond Street and Royal London hospitals, where we found 1 in 3 girls aged 11-17 years answering the survey had a problem at times. For many (if not all) girls this is rather embarrassing and many do not want to talk to their parents about it, and especially not to male doctors! It is more likely they will discuss this with female members of the team (nurse specialists, physiotherapists). We can arrange for the girls to be seen by a gynaecologist or physiotherapist, as sometimes simple 'pelvic floor exercises' can help.

9. Transplant assessment

Almost all assessments are now carried out at Great Ormond Street Hospital for Children and referrals should be made to Drs Helen Spencer or Paul Aurora. A referral proforma is available from Great Ormond Street Hospital (see below). An exception would occur in the case of an adolescent approaching transition to the adult service, in which case, the assessment should be done here, liaising with the adult team. Contact Dr Su Madge, Nurse Consultant, extension 4053 at Royal Brompton Hospital, for the booklet listing investigations. Once complete, return these to Dr Khin Gyi, Consultant in Adult Respiratory Medicine, who will discuss them with the Harefield team.

Over the years, most transplants performed in CF children were heart / lung (HLT) with the CF patient's heart being used in a domino procedure for another patient. More recently, bilateral lung transplant are being done more often. Although living lobar transplants (a lobe each from two relatives, most commonly parents) have been performed in adults and some paediatric centres abroad, they are not yet performed in paediatric practice in the UK.

Consideration of a child for HLT assessment should be based on the individual patient, and is best performed in a multi-disciplinary fashion.

Criteria for Transplant Referral

- Significantly reduced lung function, usually with FEV_1 <30% predicted. May include rapidly declining FEV_1 even if still >30% predicted.
- Severely impaired quality of life.
- Oxygen-dependent (resting SpO_2 < 90%).
- Exacerbation of pulmonary disease requiring PICU/HDU stay.
- Pneumothorax in advanced disease especially if recurrent.
- Severe haemoptysis not controlled by embolisation.
- Child and family committed to the idea.

Children fulfilling these criteria would be likely to have a median life expectancy of 2 years.

Contra-indications

The following contra-indications differ between centres, and may be subject to change over time with the availability of e.g. newer antibiotics and increasing surgical expertise. The decision will be influenced by the presence of multiple problems within an individual child.

1. Major

- Other organ failure (excluding hepatic when a lung/liver transplant could be considered).
- Untreated *Mycobacteria tuberculosis.*
- Invasive pulmonary aspergillosis.
- Malignancy in the last 2 years.
- Unstable critical clinical condition (e.g., shock, mechanical ventilation or extra-corporeal membrane oxygenation).
- Colonisation with *Burkholderia cenocepacia*.
- Child does not want the procedure despite receiving information.

2. Relative

- Long term corticosteroids > 20mg/day.
- Non-pulmonary infections e.g. Hepatitis B or C, HIV.
- Previous thoracic surgery - pleurodesis will make the procedure more difficult and should be discussed with the surgical team.
- Multi-resistant organisms e.g. NTM (esp. M abscessus), some genomovars of *B cepacia* complex, *MRSA*, panresistant *P aeruginosa*.
- Severe osteoporosis.
- Psychosocial issues/ lack of family support.
- Refractory non-adherence to current treatment.

Transplantation is so familiar to many people now from TV, newspapers etc, most of which tend to be biased towards successful outcomes, that it is often perceived as a miracle cure. It is therefore important when discussing the issues with the family and child, that as well as the potential benefits, the following negative points should be addressed (these will be addressed at the assessment meetings, but should be raised early with families):

1. Acceptance onto the waiting list does not guarantee a transplant. Due to a shortage of donors about 30% of patients will die before organs become available. The time spent with a pager waiting for organs will be extremely stressful (uncertainty, false alarms etc).

2. Heart/lung or lung transplantation is not a complete cure for CF, it is palliative. After the operation, invasive procedures including bronchoscopy and biopsies are likely to be required. In addition, unless complete eradication of reservoirs of infection has been successful (which almost never occurs due to chronic infection of sinuses), there is potential for bacterial infection of the transplanted lungs, which may make ongoing antibiotic therapy and physiotherapy necessary.

3. Transplantation has little impact on the non-pulmonary manifestations of the disease (ie, enzyme replacement and other therapies need to be continued), although there may be nutritional benefits in the medium term. CF-related diabetes may worsen.

4. Problems associated with transplantation include early rejection, severe sepsis related to immunosuppression and later development of obliterative bronchiolitis (OB). OB can eventually lead to severe respiratory impairment, and is difficult to treat successfully.

UK Paediatric Lung and Heart-Lung Transplantation

Referral Proforma

STRICTLY CONFIDENTIAL

THIS FORM MAY BE USED TO REFER TO ANY OF THE UK CENTRES THAT PERFORM LUNG & HEART-LUNG TRANSPLANTATION. PLEASE RETURN THE FORM TO THE CENTRE OF YOUR CHOICE:

GREAT ORMOND STREET
Dr Paul Aurora and Dr Helen Spencer
Cardiothoracic Transplant Office
Great Ormond Street Hospital
Great Ormond Street
London
WC1N 3JH

Tel: 020 7813 8563
Fax: 020 7813 8440

NEWCASTLE
Dr David Spencer
Cardiopulmonary Transplant Unit
Freeman Hospital
High Heaton
Newcastle upon Tyne
NE7 7DN

Office: 0191 223 1132
Fax: 0191 223 1439

GUIDANCE NOTES FOR COMPLETION OF REFERRAL PROFORMA

This proforma has been designed to streamline the referral process for potential lung and heart-lung transplant recipients. As a result potential transplant candidates can be identified more easily, be formally assessed more quickly and duplication of investigations will be avoided. The information required has been agreed by all UK lung transplant centres and this form can be used to refer to any UK centre.

Thank you for your co-operation.

KEY POINTS

Please complete all sections - any questions which are not applicable should be marked as N/A**.**

When specific results are not available but have been requested please mark as **awaited.**

Copies of Imaging (CT, coronary angiography, etc) should be sent on CD with this form

Copies of complete reports of investigations can be appended to this proforma, but the clinical summary should be completed by a member of the multidisciplinary team in the appropriate proforma section. Serial lung function tests are very helpful and should be included when available.

Any questions about this proforma or its use can be addressed by contacting the transplant co-ordinators at the hospital to which you intend to send the referral.

PERSONAL DETAILS

PATIENT NAME: ……

NHS Number:……

AGE: ……

DOB: ……

ELIGIBILITY FOR NHS CARE:……..

NEED FOR INTERPRETER: YES / NO LANGUAGE:……..

ADDRESS: ……

(Include Postcode) ……

……

TELEPHONE NUMBER ……MOBILE: ……..

REFERRING CONSULTANT:……..

REFERRING CENTRE:……..

(Include Postcode) ……

……

TELEPHONE NUMBER ……FAX: ……..

PCT: ……..

GP NAME: ……

GP ADDRESS: ……

(Include Postcode) ……

……

GP TELEPHONE NUMBER: ……FAX: ……..

IS PATIENT AWARE OF REFERRAL FOR TRANSPLANT ASSESSMENT?

YES NO (please circle)

RESPIRATORY HISTORY

Primary Diagnosis: ……

Secondary Diagnoses Respiratory……

Non respiratory 1……

2……

3……

Respiratory Diagnoses made by: Clinical /CT chest/Histology/Genotype/ Sweat Test
Details……

Any household members smoke? : YES NO (Please Circle)

Microbiology: Have these organisms ever been isolated?

Burkholderia cepacia *YES* *NO* *specimen*……date……

Pan-resistant Pseudomonas *YES* *NO* *specimen*……date……

MRSA *YES* *NO* *specimen*……date……

Mycobacteria (TB or atypicals) *YES* *NO* *specimen*……date……

Aspergillus *YES* *NO* *specimen*……date……

If YES, please give further details……

……

Oxygen at home YES NO (Please Circle)

Amount ……..L/min Average daily use …… hrs

Respiratory Past History

Haemoptysis YES NO (Please Circle)

Details: ……

Pneumothorax: YES NO (Please Circle)

Details: ……

Thoracic Surgery: YES NO (Please Circle)

Details: ……

Has the patient ever required ventilation? YES NO (Please Circle)

If yes NIV / formal ventilation in ITU (duration ……days)

Details:……

Current Exercise Capacity

Exercise tolerance …… (distance)

Formal 6 minute walk test performed? YES NO (Please Circle)

If yes Max distance …… metres Lowest saturation……%

Performed on air / oxygen at …… litres per minute

Wheelchair YES NO

Progress pre and post diagnosis (Free Text)
Include details on rate of decline, life threatening exacerbations, frequency of iv antibiotics, etc

Is family aware of prognosis? YES / NO

Is patient aware of prognosis? YES / NO

PAST MEDICAL HISTORY

Current or previous :			Details:
Heart Disease	YES	NO	……
Renal Disease	YES	NO	……
Liver Disease	YES	NO	……
Diabetes	YES	NO	……
Malignancy	YES	NO	……
GI problems	YES	NO	……
Portacath	YES	NO	……
Gastrostomy	YES	NO	……

Current Medication

1……..	Dose	Frequency
2……..	Dose	Frequency
3……..	Dose	Frequency
4……..	Dose	Frequency
6……..	Dose	Frequency
7……..	Dose	Frequency
8……..	Dose	Frequency
9……..	Dose	Frequency
10……..	Dose	Frequency

ALLERGIES:	YES	NO	(Please Circle)

1……

2……

Oral Corticosteroids?	YES	NO	(Please Circle)

Date commenced

Max dose	Current dose	Date stopped

Response……..

Family and Social History

Compliance Good YES NO (Please Circle)

Attendance Record Good YES NO (Please Circle)

Family support available:…….

Social Services input: YES NO

Details……..

School details:……..

School attendance:……..

Siblings?.....

Relevant Family Medical or Social History:……..

……
……

……
……

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……

……
……

Psychological assessment

Current or Previous History of:

Depression:		YES		NO
Panic attacks:		YES		NO
Anxiety:	YES		NO	
Needle phobia:		YES		NO
Other psychological concerns?:		YES		NO

Details ……...

……

……

……

……

……

CLINICAL INVESTIGATIONS

Weight……kgs Height……m BMI……..

ECG Date performed:

Result…… ……

Echocardiogram Date performed:

Result……...

Chest x-ray Last performed:

Result……..…

HRCT Thorax Date performed

Result……...…

……

Arterial/Capillary/Venous (please circle) Blood Gas (ON AIR)

pH …….. pO2 …….. pCO2 …….. BXS …….. HCO3 …….. Sats ……

Others (**if available**)

Bone Densitometry Spine Z score = ……..… Femur Z score = ……..…

Abdominal ultrasound ……..

Coronary angiography ……..

Right heart catheter ……..…

GORD Testing ……

Glomerular Filtration Rate ……

Respiratory Function Tests **(attach trend values if possible)**

Date	…….		…….	
	Value	%	Value	%
FEV1	…….	…….	…….	…….
FVC	…….	…….	…….	…….
FEV1/FVC	…….	…….	…….	…….
TLC	…….	…….	…….	…….
FRC	…….	…….	…….	…….
RV	…….	…….	…….	…….
TLCO	…….	…….	…….	…….
KCO	…….	…….	…….	…….

Haematology	
Date:	
Na	
K	
Urea	
Creatinine	
eGFR	
Bilirubin	
ALT	
ALP	
GGT	
Glucose (fasting)	
Chol (fasting)	
Trig (fasting)	
Total Calcium	
CRP	

Biochemistry	
Date:	
Hb	
WCC	
Platelets	
PT	
APTT	
Fibrinogen	
ESR	

Virology	
Date:	
HIV	
CMV	
Hepatitis B	
Hepatitis C	
Immunology	
IgE	

Additional Microbiology	
	Date & Details
MRSA screen	
Asp. precipitins	
Asp. culture	

Blood group (if known) ……..

Anti crossmatch antibodies (if known) YES NO

Details ……..

ANY OTHER COMMENTS

Signed…… NAME:……..

POSITION:…… DATE:……

10. Miscellaneous

10.1 Preparation for surgery

General anaesthesia commonly leads to lung atelectasis (hence post-operative fever), even in healthy patients, a situation which is exacerbated in children with CF. We therefore routinely give peri-operative antibiotics to **all CF children** undergoing general anaesthesia, however good their lung function. This includes portacath insertion, gastrostomy insertion/changes, ENT surgery such as polypectomy, tonsillectomy and also gastrointestinal endoscopy. Many of these procedures are carried out at Chelsea & Westminster Hospital but it is still important to ensure the surgeons and gastroenterologists are aware of this when arranging the procedure – always give antibiotic recommendations (IV vs oral, and choice of drug) in the referral letter.

- Minimal and moderate lung disease - (especially for minor surgery) can usually receive high dose oral antibiotics for 48 hours pre- and 48 hours post-op.
- Severe lung disease may need 7-14 days IV antibiotics pre-surgery and 7 days post-operatively, and these would be given at the Brompton. Choice of drug is determined by the latest sputum or cough swab culture. The on-call paediatric respiratory SpR at Royal Brompton Hospital will advise over the exact choice, which is usually ceftazidime and tobramycin. It is also important that chest physiotherapy is strictly adhered to during the admission.
- Children with CFRD – Discuss management prior to admission with Dr Nicola Bridges.
- Beware dehydration post-operatively leading to DIOS.
- In a non-sputum producing child see if a blind BAL can be performed by the anaesthetist if we are not bronchoscoping the child as well.

Bronchoscopy – no antibiotics beforehand but minimum 48 hours IVABs post-procedure if **significant** secretions are seen. In practice bronchoscopy often done at start of 14 day IVAB course when patient not doing well and no microbiology available or nothing ever grown. For newly diagnosed newborn screened babies, if the bronchoscopy is clear they need not stay afterwards for IVABs.

All CF patients undergoing general anaesthesia must be discussed with Dr Jane Davies (or Prof Andy Bush) re inclusion in research studies.

10.2 Immunisation

We strongly recommend that all **routine childhood vaccinations** are given at the usual times and should be arranged by the general practitioner.

Influenza immunisation for children over 6 months of age is mandatory and is also arranged by GPs. However families must be reminded and it is also useful to put a reminder in to the clinic letters to GPs in early autumn. The vaccines are usually available in October each year. If a child is receiving it for the first time, a 2nd dose is repeated 4 weeks later, otherwise it is a single injection each year. For some of the needle phobic children, we will carry out the immunisation ourselves in clinic. The vaccine is inactivated (killed) and it is given by deep subcutaneous or intramuscular injection. There are several products available, which are licensed for children over 6 months (see British National Formulary). Egg hypersensitivity

with evidence of **previous anaphylaxis** is a contraindication. Parents should also receive the vaccine.

Our experience with **H1N1 influenza** in summer 2009 and winter 2009/2010 was that our CF patients did not have particular problems and most cases were mild. Nevertheless H1N1 immunisation is recommended for all CF patients and is now included in the seasonal influenza vaccine.

Pneumococcal vaccine is not routinely recommended, as Pneumococcus is not an organism particularly associated with CF. Prevenar is now available as part of national immunisation policy, and Prevenar 13 covering 13 serotypes was introduced in April 2010. For older children however, if parents are keen, we would have no objection (Pneumovax is used for children >5 years). It is of course mandatory for children who have had a splenectomy.

Palivizumab (Synagis) is a monoclonal antibody available as passive immunisation against respiratory syncytial virus (RSV). It is given as 5x monthly intramuscular injections. There is currently no good evidence for benefit in CF and we do not routinely recommend it.

10.3 Chicken pox

Although the literature is scarce, it has been documented that varicella-zoster infection can lead to infective pulmonary exacerbations and that early treatment with aciclovir may prevent pulmonary deterioration.

Children who are not on oral corticosteroids. If the diagnosis of chicken pox is confirmed and we are contacted early in the course of the illness, we suggest a one week course of oral aciclovir in those children who are unwell and particularly those who are known to have significant chest disease (see BNFc for dose).

If however we are informed late in the course of the illness or the child really has mild chicken pox only with a few spots then aciclovir is not warranted. This is particularly the case in CF children who are well from the CF point of view.

If children are on oral corticosteroids or have recently been on them, then the Guidelines as outlined in the BNFc should be followed:

Chicken pox contacts should only receive **Varicella-Zoster Immunoglobulin** (VZIG) if:

- they have not had chicken pox previously.

and

- are currently taking oral steroids.

or

- within the last 3 months have been taking the equivalent of 2 mg/kg/day prednisolone (or >40mg/day) for 1 week *or*
- within the last 3 months have been taking the equivalent of 1 mg/kg/day prednisolone for 4 weeks.

VZIG is given by deep intramuscular injection at the following doses:
<6 years 250mg; 6-11 years 500mg; 11-15 years 750 mg; 15 years and over 1000mg.
VZIG is available directly though the Health Protection Agency (tel. 0208 200 6868).

We would also recommend that we see those children and if a chicken pox rash still develops in these children who are at risk of serious disease, IV aciclovir is indicated for at least 7 days; total 10 days treatment.

Our new screening policy is that at the 6th birthday annual review, we will measure varicella antibodies, and if negative, we will offer **varicella immunisation** (even if there is a history of having had chicken pox). There will be an initial catch up in 2011 of all older children at annual review. This is to ensure that we reduce the risk of a child contracting chicken pox while they are on a course of oral steroids for ABPA when older.

10.4 Travel abroad

Patients will need:

1. An information fact sheet which is available from the CF Trust (0208 464 7211).

2. Advice is also available in the BTS guidelines with an updated guideline from late 2010. http://www.brit-thoracic.org.uk/c2/uploads/FlightRevision04.pdf

3. Adequate travel insurance. They need to be advised to fill in the medical information in great detail so that there is no risk of the company not reimbursing a potential claim. They also need to check that the policy does not exclude pre-existing illness. CF Trust fact sheet has a list of suitable travel insurance companies. Everyone needs a European Health Insurance Card (EHIC) in order to receive free emergency care in EU countries. Information is available on http://www.dh.gov.uk/travellers.

4. All their medications (including for an extra week) plus suitable stand-by course of oral antibiotics. Remember to keep some medication in hand luggage in case of delays in airports. RhDNase will need to be carried in a cool bag.

5. Sunblock is needed if taking ciprofloxacin, doxycycline or voriconazole (and for 4 weeks after course has finished).

6. Adding extra salt to the food is usually sufficient. However if going to a very hot & dry country, salt supplements may be necessary (Slow sodium® (sodium chloride MR) 600mg (10mmol) tablets; 1 – 3 / day). This is also necessary in very hot weather in the UK.

7. In Europe (except for Cyprus, Gibraltar), the voltage for the nebuliser is not a problem (220v) and a standard travel plug adapter is all that is needed. If travelling to USA, South America, Caribbean, Cyprus, & Gibraltar, you will need a 110v nebuliser e.g. Port-a-Neb. A plug adapter is not enough. Discuss this with our Physiotherapy Department (extension 8088) well in advance of the holiday. A refundable deposit of £50 is required to borrow a nebuliser for a holiday. (A charge may be introduced at a later date).

8. Letter for customs explaining the need for all the drugs and equipment – available from the CF secretary or see appendix X.

9. Fitness to fly test needs to be considered. This consists of breathing 15% O_2 at sea level which is the equivalent O_2 concentration in the plane at altitude. It should be performed in patients with:
   - a history of oxygen requirement during chest exacerbations.
   - resting oxygen saturation < 94%.
   - FEV_1 < 50% predicted.
   - If on home oxygen, it will definitely be needed on the airplane, but a test can be used to determine flow rate necessary on the plane.

   It is arranged with lung function laboratory (extension 8910). Patients who desaturate to less than 85-90% during the test (or who have baseline FEV_1 < 50% predicted) will need oxygen available during the flight. This is especially important during long haul flights when the children are likely to sleep. Patients whose SpO_2 is normally < 92% will definitely need oxygen, and those usually on home oxygen will need an increased flow rate. Oxygen is usually available at a flow rate 2 or 4 l/min and is not humidified, arrangements can be made through the travel agents, but adequate time is needed to do so. Costs vary between airlines. Signing the letter to say a patient is fit to travel must not be undertaken lightly – it is a disaster if a plane has to be diverted if the patient was not fit! If in doubt, check with a consultant.

   Different airlines have different charges for providing on-board oxygen and these are available on the Pulmonary Hypertension Association website – http://www.phassociation.uk.com/downloads/The_Right_To_Breathe_Free_Report.pdf

   Remember that oxygen for the airport itself is not part of the airline's responsibility.

10. Additional advice to drink plenty before & during flights. Chest physiotherapy should not be forgotten during long flights.

11. Check-up in clinic prior to departure may be necessary.

10.5 Terminal Care

(Thanks to Dr Finella Craig, Consultant in Paediatric Palliative Medicine, Great Ormond Street Hospital)

Fortunately death in childhood is an unusual event amongst our CF population, although the few that do occur tend to happen in the hospital rather than at home. The overriding principal is that the child's comfort and wishes must come first followed closely by those of the immediate family. The management of a dying child needs to be flexible so as to cater for individual family needs and reviewed at least twice daily to accommodate changes in needs. We believe that communication amongst the CF team and ward staff is critical and must be consistent so as not to confuse the family.

The issue of terminal care will be discussed with the parents by the child's consultant. These discussions will include the child if possible and assuming the parents agree. We would encourage an honest and open approach at all times, although we would also consider the wishes of the child and his or her family about sharing information. It is important that a child

on the transplant waiting list receives appropriate terminal care, and is not disadvantaged by false hopes of a last minute donor organ becoming available.

Children and families should be given a choice in where their child receives care. This should include staying at the tertiary centre, going to a hospital local to the family home, going to a children's hospice and going home.

The Great Ormond Street Hospital palliative care team is able to offer 24-hour advice and symptom management support for professionals and families. This includes supporting end-of-life care outside hospital, in liaison with local and tertiary centre services (see referral information below).

Additionally the Royal Marsden team can be most helpful, and are contactable –
Joy.Ross@rmh.nhs.uk
Anna-Karenia.Anderson@rmh.nhs.uk

Do-not-resuscitate (DNR) recommendations must be discussed with the family (and when appropriate the child as well) by the consultant. Conclusions of the discussion must be documented clearly in the notes. Please refer to the Royal Brompton & Harefield NHS Trust policy document - "Do not attempt to resuscitation order in children and young people, the policy for the use of advanced statements and policy for the obtaining of consents" available on the Trust Intranet.
Should the family have decided to care for their child at home, the local paediatric & community team, as well as the general practitioner will take the lead role in the care. We would of course offer our full support, including liaison through our CF community team.

The following discusses how we handle terminal care and death at our own hospital. Please also refer to the Royal Brompton & Harefield NHS Foundation Trust policy document - "Guidelines for the management of patients and families during death and bereavement" available on the Trust Intranet.

- The GP and local paediatric consultant must be informed if a child is dying on our ward.

- The child and his or her family are given support from the medical, nursing and other members of the CF team as required. We endeavour to allow time for the family to be alone together if required - as much as essential care will allow. The individual cultural and religious needs are respected at all times, sensitive exploration of each child and family's needs are made.

- There is a hospital chaplain, Robert Thompson (020 73528121 Ext 4736), who leads a team of various faith representatives available both for consultation with staff members as well as to the child and family. Local faith leaders are welcomed if preferred by the family.

- Should the child and/or family find English speaking or understanding difficult, staff would endeavour to use professional translators regularly.

- Support for the child and family (including siblings and extended family), and the staff is offered.

- The Hospital Pain Control Team should be involved at an early stage.

- Venepuncture and other painful or uncomfortable procedures are avoided if at all possible. Intravenous access is usually unnecessary, although sometimes intravenous fluids are needed to avoid thirst if a child can not tolerate anything enterally.

- Gentle physiotherapy may be continued if it is giving symptomatic relief. It is such a way of life for most families that they may wish to continue it so that the child does not feel abandoned. The same may be true for some of the other therapies, so an individualised care plan is agreed.

- Some of the medications will be continued, although only those that offer symptomatic relief *e.g.* bronchodilators, enzymes supplements. Clearly drugs such as antibiotics, vitamins, calorie supplements etc are usually inappropriate.

- Humidified oxygen may be required.

Medication for symptom relief
See also 'Prescribing in palliative care' in British National Formulary for Children (BNFc).

1. Analgesia

- Paracetamol - oral / rectal.
  20mg/kg regularly every 6 hours (maximum 1g qds).

- Ibuprofen – oral.
  5 mg/kg (max 400 mg) regularly every 8 hours, can be given with paracetamol.

- Oral morphine.
  Starting dose is 0.1 mg/kg 4 hourly available as standard release oral solution (Oramorph) or standard release tablets (Sevredol). Dose is titrated according to response with extra doses given when necessary in addition for break through pain.

  Once requirements established, usually after 24 hours of a stable dose, this can be converted to MST (SUSTAINED release oral morphine) by dividing the total daily morphine requirements (regular + PRN) into 2 divided doses. In addition MST dose continues to be titrated to response using the standard release preparations (Oramorph or Sevredol) for break through pain. Ensure constipation is avoided by a regular laxative.

  An alternative is to start straight on MST, in which case starting dose is 1 mg/kg 12 hourly for those > 1year old, and 0.5 mg/kg for under 1 year olds, available as suspension or tablet.

- Diamorphine – subcutaneous / intravenous.
  If no longer tolerating oral MST, move on to this at a dose of **one-third** the total daily dose of oral morphine per day. Dose is then titrated according to response. If starting straight on to diamorphine, starting dose is 0.67 mg/kg/day. When given subcutaneously, use syringe driver and a small subcutaneous needle.

- Morphine – subcutaneous/intravenous
  Used if diamorphine not available. Starting dose for SUBCUTANEOUS use is HALF the total daily dose of oral morphine. For intravenous use the dose is ONE THIRD of the daily oral dose.

- Fentanyl patches or BuTrans patches should be considered. The GOSH palliative care team are able to advise on this.

2. Anxiolytic

- Diazepam – oral / rectal. Oral 1 month – 1 year: 0.5mg/kg TDS; 1 – 4 years: 5mg TDS; 5 – 12 years: 10mg TDS; >12 years: 6-30mg TDS.

- Midazolam - subcutaneous / intravenous. Sedating and amnesic effect as well. Can be mixed with diamorphine & cyclizine (see BNFc). Initial dose for >1 year is 250 – 1000 mcg/kg/day. Adult dose is 20-100mg / 24 hours.

- MST or morphine should also offer relief (see above for dose).

- Methotrimeprazine (levopromazine) – oral / subcutaneous (see below for dose).

3. Anti-emetic

- Cyclizine – oral / IV
  May be 1st line if central element to nausea. Dose (same for oral & IV) is 25 mg 8 hourly aged 6-12 years, 50 mg 8 hourly if > 12 years. Under 6 years use 1 mg/kg 8 hourly (not licensed). It may also be given as a subcutaneous infusion using the total daily dose over 24 hours.

- Ondansetron – oral / IV
  Dose for <12 years is 100mcg/kg 8-12 hourly (maximum 4mg). Maximum dose >12 years is 8mg.

- Domperidone – oral
  Dose for <12 years is 200-400mcg/kg every 6-8 hours. >12 years: 10-20mg every 6-8 hours.

- Methotrimeprazine (levopromazine) – oral / subcutaneous
  If no response to cyclizine, but useful as can be given subcutaneously, and has additional anxiolytic effect. May cause some sedation as well. Initial dose for subcutaneous infusion is 0.1 mg/kg/day then dose range 0.35-3 mg/kg/day. Adult dose is 5-200mg/day. Oral dose for 1-12 years is 0.25 – 1mg/kg every 6 hours; >12 years old: 12.5-50mg every 6-8 hours. Lower doses may be as effective but cause less sedation. Can be mixed with diamorphine.

- Dexamethasone may help with nausea as well.

4. Cough

- MST or diamorphine may relieve intractable cough as given above.

5. Dyspnoea

- Humidified oxygen may help.

- MST or morphine/diamorphine may also help with dyspnoea as given above.

- Nebulised morphine has been reported as useful in a case report (Ped Pulmonol 2000;30:257-9). They used 2 mg preservative-free morphine sulphate added to 2 mg dexamethasone and 2.5 mls normal saline 4 hourly, the only adverse effect being headaches.

- Diazepam has also been used: 2 – 12 years 5-10mg TDS; >12 years 5-30mg TDS.

- Dexamethasone may help bronchospasm / airway obstruction. IV/oral dose for 2-12 years is 2mg tds and for >12 years 4mg tds.

6. Respiratory secretions

- Hyoscine patches can help but a dry mouth is unpleasant, so good mouth care is essential.
- Oral glycopyrronium may also be useful. Dose is 40-100 mcg/kg 3-4 times a day (tablets & oral liquid available on a named patient basis).

7. Restlessness / confusion / hallucinations

- Haloperidol – subcutaneous/oral.
  Can be mixed with diamorphine if lower doses used. Subcutaneous doses for 1-12 years are 25-50 mcg/kg/24 hours. Adult dose is 5-15 mg/24 hours. Oral doses for 1-12 years are 12.5-25 mcg/kg bd. Adult dose is 1-3 mg tds.

- Methotrimeprazine (levopromazine) – subcutaneous.
  See above.

8. General tonic

- Oral steroids may be useful (prednisolone 10mg or dexamethasone in an equivalent dose).

9. Syringe driver mixing and compatibility

See BNFc for more details.

Once the child has died

- The on-call SpR will need to confirm death immediately. This is done by looking for pupil reaction to light, feeling for a central pulse for 1 minute, listening for heart sounds for 1 minute, then listening to breath sounds for 1 minute.

- The family are then given the opportunity to be alone with their child for as long as they want. Alternatively they may require the presence of a member of the CF Team should they wish.

- The family may wish to take the child home after death, or transfer the child to a children's hospice local to their home. An advantage of the hospice is that the child can

stay in a cooled bedroom and parents can visit freely or even stay with their child until the funeral. If going home, particularly during hot weather, it may be necessary for the family to get air cooling units. A local funeral director may be able to help with this, or a local hospice.

- It is worth gently encouraging the family to hold their child if they wish.

- Inform the on-call consultant immediately.

- The SpR must phone the GP and local paediatrician as soon as possible and record the time this is done in the notes.

- During the normal working hours, Chris Barnes, Ward administrator PICU (extension 8590) will help provide information for the family. The other main contact is Patients Affairs Manager – Sue Ryder (extension 8036).

- On-call SpR will need to write the death certificate unless it is a coroner's case (this is most unlikely with an expected death of a CF patient).

- Mandatory reporting. If a death is unexpected contact Dr Paul Hargreaves or Dr Kingi Aminu at Chelsea & Westminster Hospital as they are our local SUDI paediatricians. Far more likely is that deaths are anticipated, in which case no need to inform them. But we still fill in Initial Notification Forms A & B ensuring the box 'expected' is ticked, and send to the single point of contact.

- Parents will need to make an appointment at Chelsea Old Town Hall (0207 351 3941) to register the death. They will need the death certificate in order to do this.

- They should be given the Hospital Trust leaflet entitled 'When Your Child Dies'.

- If a child has an expected death at home and the parents ring the ward, they must be told to phone their GP or community nurse when they feel able. If it is during the night they may want to wait until morning when the surgery opens. A death certificate will usually only be issued by their own GP, the next working day. If they want a funeral director to move the child before a death certificate is issued, they need written confirmation of death from a doctor (usually the duty GP if out-of-hours) or a nurse (usually the community children's' nurse). The on-call consultant must be informed immediately.

- The CF nurse specialist is responsible for ensuring all members of the CF team are informed the child has died. She will also ensure Out-patient Administrators are informed so that appointments are no longer sent to the family.

- Another invitation given routinely is to the hospital commemorative ceremony for children who have died. This is an annual event, comprised of words and music, open to those of any or no religion. Although the hospital chaplaincy and other religious leaders come, there is no overt religious content. Parents chose music their child loved, or a reading, or ask for a poem they have themselves written. The reading may be given by the parents themselves, by a sibling or a friend or staff member. A brief talk is given by a senior member of staff, and a brief closing ceremony such as the release of balloons ends the occasion. Refreshments are served.

- Bereavement counselling will be offered to the family. They will be invited (by letter) to come back to discuss any issues with a consultant in 4-6 weeks.

Palliative Care Support

Any child and family with a palliative care need can be referred to the Great Ormond Street Palliative Care Service. This is an outreach service. The team can be contacted through the Great Ormond Street switchboard 020 7405 9200: ask to aircall the palliative care team. The direct line to the office (Mon-Fri 9am –5pm) is 020 7829 8678.

Transport Home of a Child's Body from RBH

A child's body can be removed from the hospital at any time unless there is a legal requirement for a post mortem. The family may wish for the child to go home, to a relative's house or to a hospice.

A parent can take a child's body home.
A Death Certificate must be given to the family before they leave.
A covering letter from a doctor or another medical member of staff is required.
The exception to this is if the child is travelling outside England or Wales where the Coroner must provide an Out of England Certificate prior to travel.

The family may wish to move the child themselves. If so:

1. Ensure they are given the death certificate
2. Give them a letter (written by a doctor or nurse) stating
    a. Date
    b. Childs name, date of birth and that the child has died
    c. Address they are travelling from
    d. Address they are travelling to
    e. Car registration number and name of driver
3. Legally, a body must be transported "in a suitable container". We interpret this as meaning that children must be safely secured in a car seat, as they would be if alive (to prevent injury to other passengers in a collision)

If parents want the child to go home or to a hospice, but are unable to transport the child themselves, there are several options:

1. Contact a funeral director (either local to the family or local to the hospital). They will be able to arrange transfer of the child and can usually act fairly quickly. Normally parents bear the cost of transport of their child's body as part of the bill for the funeral, if a Funeral Director is used.
2. The hospice may be able to arrange to collect the child
3. The family may have a friend/relative who can help
4. See if hospital transport can assist
5. St John's Ambulance or the Red Cross may be able to assist.
6. NB. London Ambulance Service DOES NOT perform this service

Don't forget that a covering letter must be provided for any driver other than a Funeral Director, and parents must be given the Death Certificate before they remove their child's body.

11. Drug Formulary

11.1 Drugs for the respiratory tract

In CF, doses of antibiotics are usually given at a higher dose and for a longer period than in non-CF children, for reasons of pharmacokinetic differences as well as the presence of underlying lung disease. See section 6.2a for antibiotic prescribing policies.

NOTE: **od = once daily; bd = twice daily; tds = 3 times daily; qds = 4 times daily**

11.1a PROPHYLACTIC antibiotics

Oral

Augmentin Duo	Oral Susp (400/ 57)	2 months – 2 yrs 0.15 ml/kg bd; 2-6 yrs 2.5 ml bd 7-12 yrs 5 ml bd	Use if flucloxacillin not tolerated or regularly grows *H influenzae*. Tastes better than flucloxacillin but may discolour teeth more than flucloxacillin. **Clean teeth after dose**.	Augmentin duo is suspension only and is used for those who cannot take tablets. If want tablets, use standard augmentin 375 mg (250/125) tabs.
Augmentin (co-amoxiclav)	Oral tabs (250/ 125)	>6 yrs 1x (375 mg) tab bd		
Azithromycin	Oral	<15kg: 10mg/kg od 15-40 kg: 250mg od >40kg: 500mg od	**Consultant decision.**	*Potential* for hepato- and ototoxicity but usually *very* well tolerated. Can cause tooth and tongue discolouration.
Flucloxacillin	Oral	3-5kg: 125mg bd 5-9kg: 175mg bd 9-15kg: 250mg bd Older children: 25 mg/kg bd	Give 1 hour BEFORE meals or on an empty stomach. Liquid tastes awful – different brands may be tolerated better than others.	If *S aureus* a troublesome, regular problem can use up to 2 g bd **– Consultant decision.**

Nebulised

Amikacin (from IV solution)	Nebulised	6-12 years: 250mg bd >12 years: 500mg bd		Can further dilute injection with 0.9% sodium chloride
Amphotericin (Fungizone)	Nebulised	<10 years 5 mg bd >10 years 10 mg bd Dose can be increased up to max 1mg/kg/day (Max 25mg bd) depending on clinical response and tolerability. Dilution: 50 mg in 10ml of water. For a 5 mg dose, use 1ml of this solution and dilute further with 2ml of water (minimum volume of 3ml for nebulisation).	For chronic aspergillus.	**Consultant decision**. Use 1 vial per day, keep remaining solution in the fridge. No need to use expensive liposomal preparation unless cannot tolerate standard preparation.
Aztreonam Lysine (Cayston)	Nebulised	75 mg tds for 28 days Not licensed in <18 years *Not yet approved for use at RBH.*		**Consultant decision.** PCT funding required prior to initiation.
Ceftazidime	Nebulised	1 gm bd Reconstitute 1 gram injection with 3ml water for injection	For *B cepacia*. Tastes awful.	**Consultant decision**
Colistin	Nebulised	<2 yrs: 500,000 Units bd 2-8 yrs: 1,000,000 Units bd >8 yrs: 2,000,000 Units bd 1,000,000 units = 1 megaunit See physio section 6.14 for doses of Promixin in an iNeb, which are half those of colomycin given in a standard nebuliser.	Bronchospasm can be reduced by i) diluting with water, and ii) pre-dose with bronchodilator. **1st dose in hospital with spirometry pre- and post-dose.**	This is now used alone as standard therapy – so the old standard doses have been doubled. However use half these doses if still combined with gentamicin. Minimum volume for nebulisation is 3mls.
Gentamicin (from IV solution)	Nebulised	<2 yrs: 20 mg bd 2-8 yrs: 40 mg bd >8 yrs: 80 mg bd	Dose can be doubled in certain circumstances. Blood levels not necessary.	No longer used routinely. But when given, is combined with colomycin – can be mixed together (use immediately). Minimum volume for nebulisation is 3mls.

Meropenem (from IV solution)	Nebulised	6-12 years: 125mg bd >12 years: 250mg bd		Reconstitute 500mg vial with 10ml 0.9% sodium chloride (keep remainder of vial in fridge for up to 18 hours).
Tobramycin - Bramitob or TOBI	Nebulised	300 mg bd during **ALTERNATE MONTHS** Licensed >6 years only		**Consultant decision. C**olomycin will usually be given in the month off TOBI

11.1b Oral antibiotics for TREATMENT of a pulmonary exacerbation.

See section 6.2a for antibiotic prescribing policies. Decision depends on:

- Current clinical state.
- Current and past organisms and their antibiotic sensitivities.
- Past history of individual.
- Known 'allergies' or intolerance.

Augmentin Duo	Oral susp (400/ 57)	2 months – 2 yrs 0.3 ml/kg bd; 2-6 yrs 5 ml bd 7-12 yrs 10 ml bd	For *S aureus* and *H influenzae* Care with CF liver disease	Augmentin duo is susp only. Augmentin 625mg tabs can be used for those who can take tablets. Augmentin 625mg tabs are to be used in preference to 2 x 375mg tabs to reduce clavulanic acid intake.	One month
Augmentin (co-amoxiclav)	Oral tablets (500/ 125)	>6 yrs: (625mg tabs) 2 tabs mane & 1 tab nocte			
Azithromycin	Oral	10 mg/kg od max 500 mg	*S aureus*, *H influenzae* and *mycoplasma*		Ten days gives about 1 month's coverage.
Chloram-phenicol	Oral	>1 month 12.5 mg/kg qds. Occasionally use 25 mg/kg qds (Max 4 gms/day).	Consider with *S maltophilia, P aeruginosa, B cepacia, S aureus* and desperation.	Needs full blood count at day 21 if course longer than 3 weeks. Now very expensive (£400 - £1500 per two week course) Preferably round dose to the nearest whole capsule. Capsules can be opened and the contents mixed with water or orange juice.	2-3 weeks

Ciprofloxacin	Oral	<1 y 15 mg/kg bd ≥1yr: 20 mg/kg bd (max 750mg bd). Care should be taken if previously used within previous 3 months because of risks of resistance.		**First line** oral antipseudomonal agent. Photosensitising so warn patient re sunlight. High strength sunblock should be used in summer or on holidays for 4 weeks after course finished. Joint pains occasionally – risk of tendonitis and tendon rupture – consider withdrawing treatment Milk **will** reduce absorption. Avoid milk for at least 30 mins before and after taking ciprofloxacin.	**3 weeks for 1st isolation.** **Consultant decision** to exceed this period. Also used for NTM treatment – **consultant decision**
Clarithromycin	Oral	1-2 yrs – 62.5 mg bd 3-6 yrs – 125 mg bd 7-9 yrs – 187.5 mg bd >10 yrs – 250 mg bd		Cheaper alternative to azithromycin. Can cause tooth and tongue discolouration. Part of NTM protocol.	One month
Co-trimoxazole	Oral	6 weeks–5 months: 120 mg bd 6 months–5 years: 240 mg bd 6–11 years: 480 mg bd 12–18 years: 960 mg bd		Use mainly for *S maltophilia.* Maintain adequate fluid intake Treatment should be stopped if blood disorders or rashes develop. Advise patient/carer to report all rashes, sore throats and fevers. Avoid in severe liver disease.	One month
Doxycycline	Oral	>12 years: 200 mg **once daily** on day 1 then 100 mg once daily thereafter (can increase to 200 mg daily if required).	Can be useful for *S maltophilia* and *B cepacia*, and MRSA **Consultant decision.**	Patient MUST be > 12 years (due to discoloration of growing teeth and bone). Take standing or sitting upright with 200 ml water (to avoid oesophageal irritation). Photosensitivity (see ciprofloxacin).	2-4 weeks (can be used long term
Ethambutol	Oral	15mg/kg od (max 1.5g od)		Consultant decision – reserved for the treatment of NTM See appendix II. Monitoring - Visual acuity	

Flucloxacillin	Oral	50 mg/kg bd Can give total daily dose in 3 divided doses	Give 1 hour BEFORE meals or on an empty stomach. Liquid tastes awful – different brands may be tolerated better than others.	Can use up to 2 g bd – **Consultant decision.**	One month
Fusidic acid	Oral	<1 yr: 15mg/kg (0.3ml/kg) tds 1-5 yrs 250 mg tds (5 ml) 6-12 yrs 500 mg tds (10 mls) > 12 yrs 750 mg tds (15mls) **or** 500mg sodium fusidate tablets tds		See rifampicin. Caution in CF liver disease. Take with or after food Should always be prescribed with additional anti-staphylococcal agent Higher dose of fusidic acid liquid needed as incomplete absorption compared to sodium fusidate tablets.	Two weeks
Linezolid	Oral	<12yr. 10mg/kg (max 600mg) **tds.** ≥12yr 600 mg bd	Last line for *MRSA* or *S aureus* where patients have not responded to conventional agents e.g. high dose flucloxacillin, rifampicin, fusidic acid. **Consultant decision.** Courses >28 days leads to risk of optic neuropathy so patients having 4 week or repeated courses should have ophthalmic exam before starting first course and every 2 months after. Aim for 2 week courses. Where possible patients should be warned to immediately report any visual changes, regardless of treatment duration. Monitor FBC weekly.		
Minocycline	Oral	>12 years: 100mg **bd**	Can be useful for *S maltophilia.* **Consultant decision.**	Patient MUST be > 12 years (due to discoloration of growing teeth and bone). Caution in CF liver disease. Take standing or sitting upright with plenty of water (see doxycycline).	Two weeks

Rifampicin	Oral	10 mg/kg (max 600mg) bd.	Second line for *S aureus*. Usually give with fusidic acid.	Give 30 – 60 minutes ***before*** food. **Consultant decision.** Caution in CF liver disease. Please note rifampicin interacts with many drugs (including itraconazole, voriconazole, chloramphenicol) so always check in BNFc. Can cause red staining of urine, tears and saliva	Two weeks See appendix II.

11.1c INTRAVENOUS antibiotics for treatment of a pulmonary exacerbation.

See section 6.2a for antibiotic prescribing policies. Decision depends on:

- Current and past organisms and their antibiotic sensitivities.
- Past history of the individual patient.
- Known 'allergies' or intolerance.

NOTE

i) Two antipseudomonal antibiotics from different classes are ALWAYS given – consultants only for exceptions.

ii) High dose flucloxacillin is usually given by mouth as it ruins long lines and is well absorbed orally. This is automatically given when *S aureus* has been grown in the past year but for other patients discuss with the consultant on admission.

iii) Preferred *blind* starting combination is meropenem (better Staph cover) or ceftazidime (or aztreonam) **plus** tobramycin (gentamicin should be avoided due to increased renal toxicity and less favourable MIC) **plus** oral flucloxacillin/augmentin.

iv) Course length is **always** a minimum two weeks.

v) Take care with first doses as unexpected, severe hypersensitivity does occur.

vi) Round doses up or down for ease of administration, especially for home IVABs (See CIVAS dosing tables below).

vii) Antibiotics can impair liver and renal function. Take care with drug dosing with underlying impairment – refer to BNFc or the pharmacy team for more information.

CIVAS (Centralised Intravenous Additives Service)

Following introduction of CIVAS pharmacy made up IV antibiotics at RBH, dose banding to ease calculations and reduce waste has been introduced for AZTREONAM, CEFTAZIDIME, MEROPENEM, PIPTAZOBACTAM, METRONIDAZOLE and COLISTIN. Please see below (page 101) for the CIVAS dose banding tables. This is VERY important for RBH staff.

Nurses will fax the CIVAS order form to Pharmacy once the drug is prescribed on the usual IV drug chart. This form must be faxed by **9.30 am Mon-Fri** (for doses to be ready by 4pm), so it must be prescribed by then and the nurse in charge informed. Since most patients come in for admission during the daytime, the dose for that night and the next morning is made up by the nurses in the usual way on the ward. Admissions from Friday daytime, Saturday & Sunday (and bank holidays) will receive drugs made up on the ward until evening of next midweek working day.

If a child is definitely coming in the next day (confirmed with parents and bed definitely free), then CIVAS can be prescribed by 9.30 am on the day of admission *ie* before they arrive. Antibiotic choice will be based on latest sputum culture; check notes to ensure no antibiotic allergies plus any past problems with aminoglycoside levels. Check recent weight. Bed coordinators will liaise with paediatric pharmacists in advance.

Because of short expiry times, amikacin, meropenem and colistin cannot be made up by CIVAS to last a full weekend. Unless critical, do not change antibiotics over weekends when CIVAS unavailable.

Amikacin	IV	30 mg/kg od (max 2g od)	Infuse over 30 mins. Levels at 23 hours after 1st dose (ie **before** 2nd dose) must be < 3mg/l. Repeat at least every 7 days. If level raised, OMIT next dose and re-measure, reduce dose by 20%. See section 6.2a	Aminoglycoside	Only use if resistant to tobramycin or gentamicin. Dilution: 0.9% sodium chloride. Used for initiation of NTM treatment – consultant decision
Aztreonam	IV	75 mg/kg tds (Max 8 gms /day).	No gram-positive activity.	Monobactam	Usual reconstitution: water for injections.
Cefoxitin	IV	200mg/kg/day in 3-4 divided doses (Max 12g /day).	Can give as a slow bolus or infusion over 30 minutes.		Reserved for treatment of NTM – consultant decision See appendix II.
Ceftazidime	IV	50 mg/kg tds (Max 9 gms /day). Can use total dose in two divided doses at home.	Unexpected hypersensitivity on first exposure.	Cephalosporin	Usual reconstitution: water for injections.
Colomycin	IV	20,000-25,000 units/kg **tds**. **Long term use at home:** Use above total daily dose divided into 2 doses i.e. (30,000-38,000 units/kg **bd**) Boluses can be used for **Portacaths** only – not PICC lines. For home use only. <12 yrs: dilute to 90,000 units/ml. 12 yrs +: dilute to 200,000 units/ml.	For in-patients we use slow infusion over 30 mins. Measure renal function once a week. Maximum concentration 40,000 units/ml. May use up to 2MU tds if desperate in those >40kg **Consultant decision**.	Polymyxin	Not a first line agent**.** **Avoid using with IV amphotericin** (renal toxicity)**.** Usual reconstitution: 0.9% sodium chloride

Linezolid	IV	<12 years: 10mg/kg (max 600mg) tds ≥12 years: 600mg bd	Infuse over 30 – 120 mins. Monitor FBC weekly. **Consultant decision only as courses >28 days leads to risk of optic neuropathy so patients having alternate monthly Linezolid should have ophthalmic exam before starting first course and every 2 months after.** Where possible patients should be warned to immediately report any visual changes, regardless of treatment duration.	Oxazolidinone	Use oral route wherever possible. Otherwise convert to oral route as soon as clinically indicated. Last line for *MRSA* or *S aureus* where patients have not responded to conventional agents.
Meropenem	IV	20 – 40 mg/kg tds. Max 2g tds	Headache common.	Carbapenem	Usual dilution: water for injections.
Tazocin = Piperacillin/ Tazobactam	IV	>2 months: 90mg/kg qds (Max 4.5g qds)		Ureidopenicillin	**Consultant decision.** Not used unless we are desperate due to rashes and hypersensitivity.
Teicoplanin	IV	10mg/kg 12 hourly for 3 doses (loading dose) followed by 10mg/kg od.	Can give as a slow bolus or infusion over 30 minutes	Glycopeptide	Consultant decision
Temocillin	IV	25mg/kg bd Max dose 2g bd		Penicillin	Consultant decision. 3rd line Dilution: water
Tigecycline	IV	1mg/kg bd (max 50mg bd)	Infusion over 30 to 60 minutes. Nausea/vomiting a real problem. Use regular oral Ondansetron.	Tetracycline	Reserved for treatment of NTM – consultant decision. See appendix II.

Timentin = (ticarcillin/ Clavulanic acid)	IV	80-100 mg/kg qds. Max 3.2 gms qds	Infusion over 30 mins.	Carboxy-penicillin	**Consultant decision.** Kept for ***B cepacia*** and desperation. Usual dilution: water for injections.
Tobramycin	IV	10mg/kg/day in ONE DOSE Max dose: 660mg/day. If previous course had raised trough level reduce dose by 20%	Infuse over 30 mins. Levels at 23 hours after 1st dose (ie **before** 2nd dose) must be <1 mg/l) Repeat at least every 7 days. If level raised, OMIT next dose and re-measure. See section 6.2a	Aminoglycoside	Usual dilution: 0.9% sodium chloride.

We RARELY use:

i) Imipenem - too many side effects and spectrum no different from meropenem.

ii) Piperacillin/tazobactam (Tazocin, piptazobactam) is rarely used because there is a high incidence of allergy.

CIVAS Antibiotic Dose Bands

The dose bands and intervals stated below may not be suitable for patients with **renal and/or liver impairment**. Please contact the Pharmacist for advice on dosing in these circumstances.

Patient Weight (Kg)	Aztreonam (Dose TDS)	Ceftazidime (Dose TDS)
<15	75 mg/kg	50 mg/kg
15 - 17	1.2 grams	750 mg
18 - 21	1.4 grams	1 gram
22 - 25	1.8 grams	1.2 grams
26 - 30	2 grams	1.4 grams
31 - 35	2.4 grams	1.6 grams
36 - 40	2.6 grams	1.8 grams
41 - 45	2.6 grams	2 grams
46 - 55	2.6 grams	2.5 grams
56 & above	2.6 grams	3 grams

Patient Weight (Kg)	Meropenem (Dose TDS)	Metronidazole (Dose < 1 month BD; > 1 month TDS)
<10	20 - 40 mg/kg	7.5 mg/kg
10 - 12	20 - 40 mg/kg	85 mg
13 - 15	500 mg	100 mg
16 - 20	500 mg	125 mg
21 - 25	750 mg	175 mg
26 - 30	1 gram	200 mg
31 - 35	1 gram	250 mg
36 - 40	1 gram	300 mg
41 - 50	1.5 grams	500 mg
51 & above	2 grams	500 mg

Patient Weight (Kg)	Colistin (Dose TDS)	Piperacillin Tazobactam (Dose < 2months BD; > 2months TDS-QDS)
<15	20 – 25,000 units/kg	90 mg/kg
15 – 17	380,000 units	1440 mg
18 – 20	450,000 units	1575 mg
21 – 25	500,000 units	2025 mg
26 – 30	630,000 units	2475 mg
31 – 35	800,000 units	2925 mg
36 – 40	800,000 units	3375 mg
41 – 45	1 Mega Unit	3825 mg
46 - 50	1 Mega Unit	4275 mg
51 - 60	1,300,000 units	4500mg
61 - 80	1,500,000 units	4500mg
80 & above	2 Mega Unit	4500mg

Other drugs supplied by Pharmacy CIVAS that are not dose banded:

- Gentamicin
- Amikacin
- Tobramycin
- Linezolid
- Liposomal Amphotericin (Ambisome®)

Please prescribe them using the usual mg/kg doses as stated in RBH paediatric medicines reference sources (i.e. Trust Guidelines, BNFc)

Any other antibiotics not stated above are not available from the Pharmacy CIVAS and should be prescribed in the usual way.

11.1d Antifungal therapy

Itraconazole	Oral	1month – 12 yrs: 5 mg/kg twice daily (max 200mg bd) >12yrs 200 mg twice daily	Must be used when treating ABPA with steroids, when taking steroids for whatever reason if aspergillus isolated, and for symptomatic aspergillus infection. See section 6.6. Poorly absorbed, use liquid, on empty stomach if possible. Capsules should be taken with acidic liquid e.g. **coca-cola** and **food**. Stop antacids if possible. We now give the once daily dose twice daily. Headaches seem commonest problem but in theory hepatotoxic. Adrenal suppression also been seen when combined with budesonide. Do liver function tests if taken >1-2 months or if known liver dysfunction. See BNFc. Note interaction with rifampicin. See section 6.8 for levels	See **section 6.6** for length of courses.
Voriconazole	Oral	**>2years: – 12 years:** 200mg BD (Liquid preferred) **>12 years:** <40kg 200mg bd for 1 day then 100mg bd (max 150mg bd) >40kg 400mg bd for 1 day then 200mg bd (max 300mg bd).	May be used for ABPA where patients have not responded to or are intolerant of itraconazole. **Consultant decision and microbiologist approval required.** See section 6.5 Take on an empty stomach. Monitor liver function tests + FBC monthly. Highly Photosensitising so warn patient re sunlight. High strength sunblock should be used in summer or on holidays for 4 weeks after course finished. See section 6.8 for levels	See **section 6.8** for length of courses
Liposomal amphotericin (Ambisome)	IV	5 mg/kg od Start at 1 mg/kg once daily then increase to 5 mg/kg od over 3 days. Give test **dose** of 100 mcg/kg (max 1mg) over 10 mins. Observe for 30 mins then continue Treatment.	For invasive or troublesome aspergillus. Check **renal/liver function and U&Es at least 3/week. Use with caution with other nephrotoxic antibiotics** e.g. aminoglycosides, colomycin. We DO NOT use standard IV amphotericin preparation.	**Consultant decision**. Administer over 30 mins. Compatible with 5% Dextrose only. Flush pre & post dose with 5% dextrose. Final concentration of the solution should be 0.2 – 2 mg/ml.

Caspofungin	IV	<3 months: 25 mg/m^2 3months - 1yr 50 mg/m^2 >1 yr 70 mg/m^2 (max 70mg) day 1 then 50 mg/m^2 (max 70mg). This can be increased to 70 mg/m^2 (max 70mg) if lower dose is tolerated but inadequate response	For invasive or troublesome aspergillosis. 3rd line agent for those intolerant, or inadequate response to liposomal amphotericin. Reduce dose in liver impairment (see BNFc). VERY expensive. 50 mg vial = £327.	**Consultant decision.** Infuse over 60 mins. Dilute to concentration not exceeding 500 mcg/ml with 0.9% sodium chloride. Incompatible with glucose solutions.

11.1e Other respiratory treatments

Azithromycin (see 11.1a & 11.1b for standard antibiotic use)	Oral	250 mg od, 15-40 kg 500 mg od, >40kg After 6 months reduced down to Monday, Wednesday and Friday only	Potential long-term treatment as anti-inflammatory. **Consultant decision**	*Potential* for hepato- and ototoxicity but usually *very* well tolerated. No additional anti-staph prophylaxis needed when maintained on this long term (unless macrolide resistant). **Avoid** long term concurrent use with erythromycin
rhD.Nase	Nebulised	2.5 mg once daily for 1st 3 months, then 2.5 mg alternate days	In afternoon, **at least 1 hour pre-physiotherapy.** Can be given at bedtime (see section 6.4).	3 month trial to assess effect. Occasionally use twice daily - **consultant decision.**
Hypertonic saline 3.5 - 7% (Nebusal 7% 4ml single dose ampoule).	Nebulised	2-4 mls up to twice a day 30 mins pre-physiotherapy	Occasionally very beneficial. Pre-treat with bronchodilator. (see section 6.5).	Consider if rhDNase fails. For 3.5% solution: dilute 7% solution with an equal volume of water for injections

11.2 Drugs for the gastrointestinal tract

11.2a Pancreatic Enzymes

- Get to know one preparation properly. This clinic uses **Creon Micro (for infants) or Creon 10,000** for all children except under exceptional circumstances. See section 7.2 on PERT.
- Dose for a child is *approximately* 1 capsule per 3-5 grams of fat.
- In babies, start with ½ capsule per feed (½ capsule per 6-8 g fat) mixed with expressed breast milk, infant formula or apple puree*, just before feeds and increase in half capsule steps (quarters is too fiddly).
- Enzymes may not be chewed or *mixed into* food, avoid mixing into hot foods
- Dose should not exceed 10,000 units/kg/day of lipase without considering why needed.

Creon Micro	=	5,000 units of lipase per scoop
Pancrex V powder	=	25,000 units of lipase per gram
Creon 10,000	=	10,000 units of lipase per capsule
Creon 25,000	=	25,000 units of lipase per capsule
Nutrizyme 10	=	10,000 units of lipase per capsule

***NOTE:** Current WHO guidelines do not recommend the introduction of solids in infants less than 6 months (or 17 weeks at the earliest). At RBH we use apple puree to provide enzymes from birth as the puree keeps the enterically coated enzyme spheres in a gel. This ensures that the child takes in the entire dose, and minimizes the chance of gum breakdown caused by trapped enterically coated spheres in the mouth. If apple is not available, other fruit purees may be used. If apple purees for enzyme administration are introduced from birth, they must be done so carefully.

11.2b Fat soluble vitamins

Empirically, the aim is to have plasma levels of vitamins A and E at upper limit of normal range. Daily recommendations from the CF Trust Nutrition Working Party are:

Age	**Vitamin A** *1 mcg = 3.3 IU*	**Vitamin D** *1 mcg = 40 IU*	**Vitamin E**
< 1 Year	1200 mcg (4000 IU)	10 mcg (400 IU)	10 - 50 mg
> 1 Year	1200 - 3000 mcg (4000 –10,000 IU)	10 - 20 mcg (400 – 800 IU)	50 – 100 mg
Adults	1200 - 3000 mcg (4000 –10,000 IU)	20 – 50 mcg (800 – 2000 IU)	100-200 mg

Preparations:

- **Dalivit**: 1.2 ml supplies 3000 mcg of Vitamin A, 20 mcg of vitamin D, and **no** vitamin E.
- **AquADEKs™** are a brand of all-in-one multivitamins designed for people with CF. We do not use this product at the Royal Brompton. They are large and have a reputation for causing nausea. If parents particularly wanted to use this product they should discuss with their doctor or a member of the team. They may be prescribed by the GP (a letter to the

GP is required requesting them to start treatment) or it is available to buy over the counter as a food supplement.

- Abidec: not usually given due to low vitamin A content however may be a suitable alternative if Dalivit unavailable.
- One **adult multivitamin tablet BPC** contains: Vitamin A 800 mcg, Vitamin D 7.5 mcg, Vitamin C 15 mg + Vitamin B and **no** vitamin E – **so not now recommended**
- One **Vitamin A + D Capsule BPC** contains: Vitamin A 1200 mcg, Vitamin D 10 mcg.
- Vita-E gel capsules: 200 unit capsules ≈ 134mg Vitamin E
  400 unit capsules ≈ 268mg Vitamin E

Recommendations (empirical):

Birth to 1 year:	**Dalivit** 0.6 ml + **Vitamin E** 50 mg (0.5ml) (= Vit A 1,500mcg,Vit D 10 mcg)
>1 to 4 years:	**Dalivit** 1.2 ml + **Vitamin E** 100 mg (1ml) (= Vit A 3000mcg, Vit D 20 mcg)
>4- 8 years:	**Dalivit** 1.8 ml + **Vitamin E** 100 mg (1ml) (= Vit A 4500mcg, Vit D 30 mcg)
> 8 years	2-3 **Vitamin A+D capsules** + **Vitamin E** 100-200 mg (= Vit A 2400-3600 mcg, Vit D 20-30 mcg).

Note: annual review blood levels may not reflect dosages prescribed as low levels may simply reflect poor adherence.

Vitamin K

Offered to all children able to swallow tablets and mandatory for those with liver disease (with or without clotting abnormalities).

Use **water-soluble** preparation: **Menadiol phosphate** 10 mg od.

11.2c 'Antacids'

If enzyme dose high and compliance and diet etc have been considered then consider:

- **Ranitidine**: Birth – 6months: 1 mg/kg tds
  >6months: 2 mg/kg bd (max 150 mg bd)
  - small risk of headache.

- **Omeprazole**: 0.4-0.7 mg/kg bd (max 40 mg/day).
  Round to nearest 5mg if using dispersible 'MUPS' tablets.
  To exceed this dose ie up to 1.5 mg/kg bd is a consultant decision.
  If unable to tolerate omeprazole – lansoprazole can be tried as an alternative – see BNFc for doses.

11.2d Gastro-oesophageal reflux

Very common in CF.

- **Domperidone** 0.2-0.4 mg/kg tds
  before the 1st and middle feeds of the day and last thing at night.

Plus

- **Omeprazole**: 0.4-0.7 mg/kg bd (max 40 mg/day).
  Round to nearest 5mg if using dispersible 'MUPS' tablets.
  To exceed this dose ie up to 1.5 mg/kg bd is a consultant decision.
  If unable to tolerate omeprazole – lansoprazole can be tried as an alternative – see BNFc for doses.

  OR

- **Ranitidine** Birth – 6months: 1 mg/kg tds
  >6months: 2-4 mg/kg bd (max 150mg bd)

Consider: **Infant gaviscon**, <4.5kg: Half Dual sachet per feed; >4.5kg: one dual sachet per feed.
Erythromycin dose for gastric stasis is: 3 mg/kg tds

11.2e Distal Intestinal Obstruction Syndrome (DIOS)

Old name meconium ileus equivalent (MIE). See **section 7.5.** All therapies are osmotic in action therefore fluid support is CRUCIAL, if necessary, intravenously.

- **Oral Gastrografin**: <15 kg, 25 ml with 75 ml flavoured juice / water
  15-25 kg, 50 ml with 150 ml flavoured juice / water
  >25 kg, 100 ml with 200 ml flavoured juice / water

Do NOT give in the presence of bile stained vomiting or bowel obstruction.

- **Rectal Gastrografin**: Use same doses as oral.
  <5yrs: Dilute to 5 times its volume with water
  >5yrs: Dilute to 4 times the volume with water
  Requires IV line for IV fluids.

- Oral acetylcysteine - tastes like rotten eggs – The 200mg/ml injection can be given orally and should be mixed with water, orange juice, blackcurrant juice or coke to a concentration of 50mg/ml. Alternatively 600mg tablets are available.

1month – 2 years	0.4 - 3g STAT
2 – 7 year	2 – 3g STAT
>7 years	4 – 6g STAT

- **Klean-prep**
  - **Do NOT give in the presence of bile stained vomiting.**
  - Add contents of 1 sachet to 1 litre water – can be flavoured with a clear cordial.

- Can be given orally or via NG tube (usually latter) a single dose of domperidone 30 minutes before starting can increase gastric emptying.
- Do not administer just before bedtime due to risk of aspiration.
- Start at 10ml/kg/hour for 30 mins then 20 ml/kg/hour for 30 mins.
- If well tolerated rate can go up to 25 ml/kg/hour.
- Maximum volume is 100 ml/kg or 4 litres (whichever is smaller) over 4 hours.
- Patients must be reviewed after 1st 4 hours.
- If not passing essentially clear fluid per rectum then a further 4 hours treatment can be given.
- Maximum daily dose should be 200 ml/kg or 8 litres (whichever is smaller).
- Monitor for hypoglycaemia, which can occur with CF diabetics undergoing this regimen.

11.2f Constipation

Ensure fluid intake is adequate.

Lactulose

1-5 years: 5 ml bd
5-10 years: 10 ml bd
>10 years: 15-20 ml bd

then adjust dose according to response.

Movicol

Chronic constipation, prevention of faecal impaction:

1 - 6 years: 1 sachet of Movicol **Paediatric Plain** OD.
Adjust dose accordingly - maximum 4 sachets daily.

7 - 12 years: 2 sachets of Movicol **Paediatric Plain** OD.
Adjust dose accordingly - maximum 4 sachets daily.

13 - 18 years: Initially 1 - 3 sachets of Movicol per day in divided doses for up to 2 weeks. Maintenance dose 1-2 sachets daily.

Mix contents of each Movicol **Paediatric Plain** sachet in 1/4 of a glass (60-65ml) water and each Movicol sachet in 1/2 of a glass (125ml) water

11.2g Liver disease

- **Ursodeoxycholic acid**: 5-15 mg/kg tds
  Commonest side effect is diarrhoea (rare though), in which case, reduce dose. Last dose should be taken in late evening.

- **Vitamin K** - Menadiol phosphate 10 mg once daily.

Appendix I - Transition document: paediatric to adult care

Patient Name **Age** **Dob** **Referring consultant:** **Hosp. No. (or referring hospital):**		
	Yes/No	**Date**
TRANSITION Has transition been discussed with the patient? Has transition been discussed with parents / caregiver? Any concerns?		
Is there an agreed date of Transition Clinic?		
Have family & patient visited the adult ward? If 'no', reasons:		
FERTILITY Contraception advice given? Discussed?		
TRANSPLANTATION Has transplantation been discussed? Details of discussion:		
DIAGNOSIS Age at diagnosis: Presentation at diagnosis: **Genotype**: /		
CURRENT CLINICAL STATUS Date of measurements: Height: cms (%) Weight: kg (%) BMI: Lung function: FEV_1 (%), FVC (%), FEF 25/75 (%), SpO_2 %		
Portacath: Date: Type:		
Gastrostomy: Date: Type: Feeding regimen: Pancreatic status: sufficient / insufficient Enzyme treatment:		

	Yes/No	Date
ORGANISMS Staphylococcus aureus Haemophilus influenzae Pseudomonas aeruginosa Strenotrophomonas maltophilia Burkholderia cepacia complex, type: MRSA Atypical Mycobacteria, type: Aspergillus Other		
HOSPITALISATION How many times in the last year? Reasons for admission: No. of courses IV antibiotics (home & hospital):		
DRUG THERAPY		
ALLERGIES AND REACTIONS		
PHYSIOTHERAPY Type: Frequency: Adherence:		

COMPLICATIONS	DETAILS
Oxygen therapy Haemoptysis Pneumothorax ABPA DIOS Liver disease Varices CF-related Diabetes Arthropathy Severe small airways disease Other associated conditions	

FAMILY BACKGROUND

Parents names:

Siblings names and ages:

CF-Siblings names and ages:

CF in extended family – state relationship names and ages:

Ethnic origin:

SOCIAL SUPPORT

Disability Living Allowance: yes ☐ no ☐ Rate: Mobility: yes ☐ no ☐

EMPLOYMENT (Saturday /part-time/ weekend/full-time)

EDUCATION

Sixth Form (GCSEs, A Levels, GVNQ):
College/University:
Career interest:
Special educational needs:

HOME CARE

Have the adult homecare team been involved at any stage?
Primary Care Team:
Contact person and telephone number:

OTHER COMMENTS

Completed by: Date:

Please copy to: Charlie Hunt (c.hunt@rbht.nhs.uk)
Clinical Assistant, Adult CF Nurse Specialist Office, Royal Brompton Hospital, Sydney Street, London SW3 6NP

About Me- Please introduce yourselves to the Adult CF Team

Appendix II – Treatment of Non-tuberculous Mycobacteria (NTM)

1. Background

Nontuberculous mycobacteria (NTM) are environmental organisms with relatively low virulence, found in soil and water that are potential pulmonary pathogens increasingly affecting patients with cystic fibrosis (CF). The prevalence of NTM among CF patients, based on a recent large multicentre trial undertaken in the US, where NTM was defined as at least one positive NTM culture, is 13%. There is some evidence for an association between NTM in CF and older age, poor nutrition, increased frequency of intravenous antibiotic administration, diabetes, treatment with corticosteroids or non-steroidal anti-inflammatory drugs, allergic bronchopulmonary aspergillosis (ABPA), Pseudomonas, Staphylococcus or Aspergillus chronic infection, and deteriorating lung function, but these have not been found consistently. The commonest NTM species affecting CF patients are *Mycobacterium abscessus* (*M. abscessus*) and *Mycobacterium avium complex* (MAC); the former is the more prevalent among European Centres. The natural history of NTM disease may vary between species; several case reports suggest that *M. abscessus* follows a more fulminant course and is associated with a less good outcome.

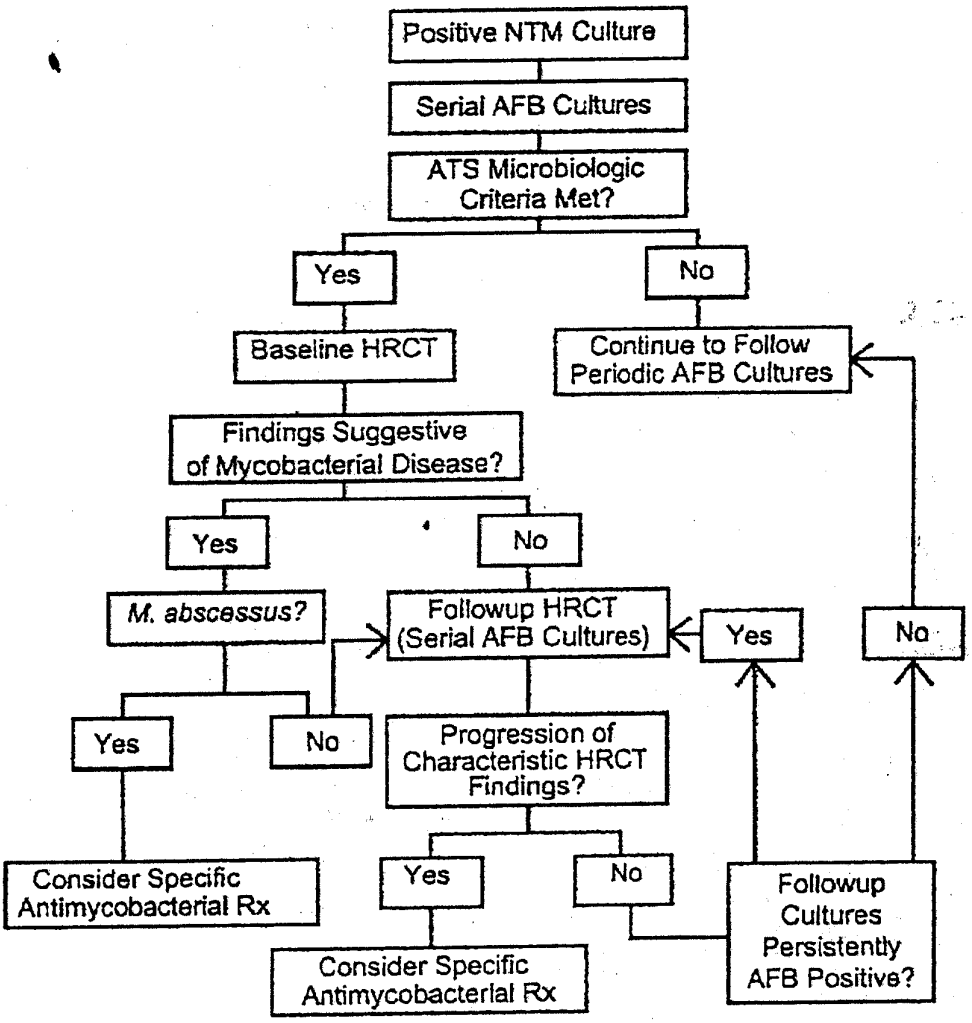
2. Indication for treatment of NTM

The presence of NTM in the sputum of patients with CF poses a significant diagnostic dilemma, as it may represent transient contamination, colonisation or infection. Not all patients will benefit from treatment for NTM. The most recent American Thoracic Society (ATS) consensus statement, although not specific to CF, provides useful guidance in evaluating NTM lung disease, and includes:

1. High resolution computed tomography (HRCT) chest scan,
2. Three or more sputum samples for acid fast bacilli (AAFB) analysis and
3. Exclusion of an alternative diagnosis.

Patients are defined as having NTM disease if they meet clinical and radiological criteria with positive cultures from two or more separate expectorated sputum samples, or from a single bronchial wash/lavage or from a biopsy with a positive culture. However, there is considerable overlap between the clinical and radiological presentation of NTM and CF per se, as well as between NTM and infection by other CF pathogens. While some patients with persistent NTM in sputum have declining clinical and radiographic parameters, this is not true of all patients. In identifying which patients require NTM treatment, it is essential that initially all non mycobacterial organisms are maximally treated. Patients should be under close surveillance and the following flow chart be used to guide treatment.

Figure 1: Flow diagram of a recommended protocol for diagnosing and treating NTM in patients with CF. (Reproduced from Olivier et al 2003(4))



Treatment should be tailored according to the specific species of NTM, which will be considered separately.

3. Treatment of *M. abscessus*

M. abscessus is universally resistant to standard antituberculous agents and no antibiotic regimen based on *in vitro* susceptibilities has been shown to produce long-term sputum conversion in patients with this organism.

3.1) Dosage and Administration

The regimen in Table 1, based on a 3 week intensive phase followed by a prolonged continuation phase, is recommended as first line therapy. If patients do not tolerate or have side effects to any of the continuation drugs, alternative agents are suggested in Table 2. Patients on first line maintenance therapy will be regarded as 'failing' treatment or relapsing if they have the following:

- Increasing sputum and breathlessness
- Fevers
- Sweats
- Rising CRP
- No response to treatment with non-mycobacterial antibiotics
- Persistent positivity on sputum AAFB smear

In this case they will be given second line intensive and maintenance treatment, as charted in Table 3.

Maintenance treatment should include four drugs in total (either nebulised or oral preparation).

If a patient is admitted with an exacerbation during their maintenance phase, then all the maintenance drugs should be continued whilst being treated with the intensive phase drugs (except minocycline/doxycycline which should be stopped if tigecycline is used).

A favourable response to treatment will be defined as when a patient is rendered sputum culture negative on serial samples collected over a period of one year. At this point the organism will be regarded as eradicated and maintenance therapy may be stopped.

Table 1. First line intensive and continuation therapy for *M. Abscessus*

Intensive phase therapy (3/52)	
Amikacin Adults Children	 IV 7.5mg/kg bd IV 30mg/kg od
Meropenem Adults Children	 IV 2g tds IV 40mg/kg (max 2grams) tds or as per CIVAS dose bands
Cefoxitin Adults and Children	 IV 200mg/kg/day in 3-4 divided doses (max 12 grams/day)
Clarithromycin Adults Children	 500mg bd orally 7.5mg/kg (max 500mg) bd orally
Continuation therapy (>/= 18/12 depending on response)	
Amikacin Adults & children >12 yrs Children over 6 years	 nebulised 500mg bd nebulised 250mg bd

Ciprofloxacin Adults Children	 750mg bd orally 20mg/kg(max 750mg)bd orally
Minocycline^ Adults and children over 12 years	 100mg bd orally
Clarithromycin Adults Children	 500mg bd orally 7.5mg/kg (max 500mg)bd orally

- If the patient has allergies to any of first line IV drugs, add tigecycline. Tigecycline should be prescribed with regular anti-emetics such as ondansetron.

Patients on long term azithromycin should discontinue it if they begin clarithromycin.

Table 2. Alternative drugs if patient is unable to tolerate or has side effects to any of the first line oral continuation drugs.

Unable to tolerate	**Drug to consider**	
Ciprofloxacin	**Moxifloxacin**[※] (adults only)	400mg daily orally
Minocycline	**Doxycycline**^ Adults and children over 12 years **Co-trimoxazole** Adults and children over 12 years Children ≥6-12 years	100mg bd orally 960mg bd orally 480mg bd orally
Clarithromycin	**Azithromycin**[#] Adults Children	500mg od orally 10mg/kg (max 500mg) od orally

[※]Avoid moxifloxacin in patients less than 18 years of age. Can be used in adults if compliance is likely to be poor

^Avoid minocycline, doxycycline and tigecycline in patients less than 12 years of age

[#]Azithromycin is recommended if compliance is likely to be poor, or if a patient is on concomitant medication which interacts with clarithromycin.

Table 3. Second line intensive and continuation therapy for *M. Abscessus*

Intensive phase therapy (3/52)	
Amikacin Adults Children	 IV 7.5mg/kg bd IV 30mg/kg **od**
Meropenem Adults Children	 IV 2g tds IV 40mg/kg tds (or as per CIVAS dose bands)
Tigecycline^ Adults Children over 12 years	 IV 50mg bd** IV 1mg/kg (max 50mg) bd
Clarithromycin Adults Children	 500mg bd orally 7.5mg/kg (max 500mg) bd orally
Continuation therapy (>/= 18/12 depending on response)	
Amikacin Adults & children>12 yrs Children over 6 years	 nebulised 500mg bd nebulised 250mg bd
Meropenem Adults & children > 12 yrs Children 6 -12 years	 nebulised 250mg bd nebulised 125mg bd
Minocycline^ Adults and children over 12 years	 100mg bd orally
Clarithromycin Adults Children	 500mg bd orally 7.5mg/kg (max 500mg) bd orally

If the patient is unable to tolerate or has side effects to the oral drugs in the second line continuation therapy regimen, consider the alternative oral agents listed in Table 2.

^Avoid minocycline, doxycycline and tigecycline in patients less than 12 years of age
**Begin tigecycline at a dose of 50mg bd or 1mg/kg bd for children. If unable to tolerate this due to vomiting the dose can be reduced to daily or alternate day dosing or 2 days out of 3. Tigecycline should be prescribed with regular IV anti-emetics such as ondansetron.

3.2) Counselling - general

- Patients will be counselled on the treatment regimen for *M. abscessus,* and its potential benefits and adverse effects. In particular they will be advised that treatment will be a

minimum of 18 months and this may not ultimately result in their becoming culture negative for this organism.
- Patients will be advised that they will receive regular monitoring throughout the duration of treatment – see individual drug monographs for details.
- Female patients of child bearing age will be advised to use adequate contraception during treatment.
- Patients will be advised to report side effects of treatment as soon as possible.

3.3) Monitoring - general
- Full blood count and the patient's renal and hepatic function must be checked prior to initiating treatment.
- Renal and liver function should be checked at 12 weekly intervals unless stated otherwise in drug monographs.
- If LFTs rise to five times the upper limit of normal at any stage, all oral drugs should be stopped. Once LFTs return to normal, each drug should be re-introduced one at a time and LFTs measured daily, as per 1998 BTS TB guidelines. This may be an indication to begin using two nebulised treatments. In re-introducing the oral drugs, begin with the one least likely to cause liver abnormalities first.

4. Treatment of Mycobacterium Avium Complex (MAC)

It is recommended that the following treatment regimen is used, which follows the ATS guidelines.

4.1) Dosage and Administration
Initial therapy should be triple oral therapy as listed in Table 2. Patients who are unwell should begin by having 2 weeks intravenous therapy with amikacin and a second anti-pseudomonal antibiotic.

Table 4. Drug treatment for MAC

Drug	**Dose**
Rifampicin	
Adults	450mg od (if <50kg) orally 600mg od (if >50kg) orally
Children	10mg/kg (max 600mg) od orally
Clarithromycin	
Adults	500mg bd orally
Children	7.5mg/kg (max 500mg) bd orally
Or Azithromycin	
Adults	500mg od orally
Children	10mg/kg (max 500mg) od orally
Ethambutol	
Adults and children	15mg/kg (max 1.5gms) od orally

4.2) Counselling - general

- Patients will be counselled on the treatment regimen for MAI, and its potential benefits and adverse effects. In particular they will be advised that treatment will be a minimum of 18 months or until they have been culture negative for a period of 12 months.
- Patients will be advised that they will receive regular monitoring throughout the duration of treatment.
- Female patients of child bearing age will be advised to use adequate contraception during treatment.
- Patients will be advised to report any potential side effects of treatment as soon as possible.
- Visual acuity should be tested using a Snellen chart before starting treatment with Ethambutol (if age appropriate).

4.3) Monitoring - general

- Full blood count and the patient's renal and hepatic function must be checked prior to initiating treatment.
- Renal and liver function should be checked at 12 weekly intervals.
- If LFTs rise to five times the upper limit of normal at any stage, all drugs should be stopped. Once LFTs return to normal, each drug should be re-introduced one at a time and LFTs measured daily, as per 1998 BTS TB guidelines.

5. Treatment of other NTM

Treatment of other NTM should be guided by the sensitivities of the organism, and should include a combination of 3 drugs.

6. References

1. CF Trust. Antibiotic treatment for cystic fibrosis: report of the UK cystic fibrosis trust antibiotic working group. 3rd Edition. May 2009

2.Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007 Feb 15;175(4):367-416.

3.Olivier KN, Weber DJ, Wallace RJ, Jr., Faiz AR, Lee JH, Zhang Y, et al. Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med 2003 Mar 15;167(6):828-34.

4.Olivier KN, Weber DJ, Lee JH, Handler A, Tudor G, Molina PL, et al. Nontuberculous mycobacteria. II: nested-cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med 2003 Mar 15;167(6):835-40.

5.Cullen AR, Cannon CL, Mark EJ, Colin AA. Mycobacterium abscessus infection in cystic fibrosis. Colonization or infection? Am J Respir Crit Care Med 2000 Feb;161(2 Pt 1):641-5.

6. Jeon K, Kwon OJ, Lee NY, Kim BJ, Kook YH, Lee SH et al. Antibiotic treatment of Mycobacterium abscessus lung disease: a retrospective analysis of 65 patients. Am J Respir Crit Care Med. 2009 Nov 1;180(9):896-902.

7.British National Formulary, 57th Edtion, Match 2009.

7. Drug monographs

7.1 Cefoxitin

Counselling
- No specific counselling required

Monitoring
- No specific monitoring required

Cautions
- Reduce dose if GFR < 20ml/minute

Contraindications
- Hypersensitivity to cefoxitin. Due to lack of data, cefoxitin should not be used in patients who are allergic to cephalosporins
- Clinical observation and laboratory data have shown a partial cross-allergy between cefoxitin, other beta-lactams and penicillins.

Interactions
- Interference with laboratory examinations: false-positive glucose parameters in urine may occur when using the reduction method. Use specific glucose oxydase tests instead
- Blood for creatinine levels should not be taken within 2 hours of a cefoxitin dose due to risk of falsely elevated creatinine levels.

Adverse effects
- Thrombophlebitis
- Hypersensitivity reactions
- Nausea and vomiting
- Diarrhoea
- Increases in serum creatinine and urea
- Transient increases in liver enzymes

7.2 Ethambutol

Counselling
- Advise patients to report any visual changes e.g. loss of acuity, colour blindness and restriction of visual fields immediately

Monitoring
- Visual acuity should be tested using a Snellen chart before starting treatment

Cautions
- Impaired renal function – reduce dose if GFR <20ml/minute
- Patients unable to understand warnings about visual side-effects

Contraindications
- Optic neuritis
- Poor vision

Interactions
- None known

Adverse Effects
- Optic neuritis
- Red/green colour blindness
- Peripheral neuritis
- Rash, pruritis, urticaria
- Thrombocytopenia

7.3 Rifampicin

Counselling
- Take 30 to 60 minutes before food
- May colour urine, tears and soft contact lenses red or pink
- Female patients taking oral contraceptives should use additional contraceptive methods

Monitoring
- Patients with pre-existing liver disease –LFTs should be measured at baseline, weekly for 2 weeks then fortnightly for 6 weeks. If liver function is unchanged, further tests are only necessary if symptoms develop
- Patients with normal liver function – measure LFTs at baseline then only if symptoms of liver dysfunction develop

Cautions
- Hepatic impairment
- Acute porphyria

Contraindications
- Jaundice
- Hypersensitivity to rifamycins

Interactions
- Clarithromycin – reduced plasma concentration of clarithromycin
- Chloramphenicol – reduced plasma concentration of chloramphenicol
- Warfarin – reduced anticoagulant effect
- Rosiglitazone – reduced plasma concentration of rosiglitazone
- Phenytoin – reduced plasma concentration of phenytoin
- Fluconazole, itraconazole, posaconazole and voriconazole– reduced plasma concentration of all, avoid using with voriconazole
- Caspofungin – initially increased then reduced levels of caspofungin, consider using increased dose
- Diltiazem, nifedipine, nimodipine and verapamil – reduced plasma concentrations
- Ciclosporin, sirolimus, tacrolimus – reduced plasma concentration, monitor levels
- Corticosteroids – reduced steroid effect, double steroid dose
- Oral contraceptives (oestrogen and progestogen containing) – reduced contraceptive effect, use other methods

Adverse Effects
- Anorexia, nausea, vomiting, diarrhoea
- Headache
- Drowsiness
- Altered liver function, jaundice
- Flushing
- Urticaria and other rashes

7.4 Tigecycline

Counselling
- Advise patient that tigecycline may cause nausea, which can be severe in some patients. Anti-emetics must be prescribed pre-emptively.

Monitoring
- Prothrombin time or other suitable anticoagulation test should be used to monitor patients if tigecycline is administered with anticoagulants.
- Biliary excretion accounts for 50% of excretion therefore patients with cholestasis should be closely monitored.

Cautions
- Cholestasis and hepatic impairment. Reduce dose in severe hepatic impairment
- Children under 18 years of age due to lack of safety and efficacy data

Contraindications
- Hypersensitivity to tigecycline or tetracyclines.
- Children under 12 years of age due to teeth discolouration

Interactions

- Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.
- Decrease in clearance of warfarin, the mechanism is unknown. This interaction is unlikely to result in significant INR changes. Monitor INR closely

Adverse Effects

- Nausea, vomiting, diarrhoea.
- Abdominal pain, dyspepsia, anorexia
- Elevated liver function tests, bilirubinaemia
- Pruritis
- Rash
- Headache

Appendix III – Antibiotic protocol for newborn screened babies in the Early Detection of Lung Disease Study.

This is the antibiotic protocol designed for all newborn screened babies who are enrolled into the above study. To avoid confusion we will treat all NBS babies the same way using this protocol.

NOTE: choice of antibiotic may vary from the protocol depending on culture sensitivities

1. Cough swabs

All infants in the study to have cough swabs done at all clinic visits, and as a minimum of 2-3 monthly using a standard protocol for collection, storage and analysis of samples.

2. Oral flucloxacillin prophylaxis dose

3 to < 5 kg	125 mg bd
5 to < 9 kg	175 mg bd
9-15 kg (~1-2 y)	250 mg bd

Based on therapeutic dose given twice daily to achieve MIC for Staphylococcus Aureus with each dose.

3. Pseudomonas aeruginosa (PsA)

3a. First growth

Cough swabs to be done at monthly intervals while on treatment.

Well child (clinical judgment), home therapy:(Frederiksen, Koch, and Hoiby 330-35)

- Oral Ciprofloxacin 15mg/kg bd for 3 weeks, PLUS
- Nebulised Colistin 1 mu bd for 3 months

Unwell child (clinical judgment), hospital therapy –

The choice of the initial IV antibiotics will be independent of sensitivities and if necessary tailored once sensitivities are known.

- IV tobramycin 10 mg/kg once daily for 2 weeks (trough level 23 hours after 1st dose, must be < 1 mg/l), PLUS
- IV ceftazidime 50 mg/kg three times a day

- Also start nebulised Colistin 1 mu bd for 3 months, (initiated in hospital as appropriate).

3b. Re-growth during the initial 3 month treatment period (whilst still on colistin)

Well child

- Give a further 3 weeks Ciprofloxacin 15mg/kg bd for 3 weeks

Unwell child

- IV Tobramycin and Ceftazidime for 2 weeks then further 3 months nebulised colistin (doses as above).

- OR If IV antibiotics already given at 1st isolation, can give 3 weeks ciprofloxacin and further 3 months nebulised colistin (if 2nd IVAB course inappropriate).

3c. Regrowth at end of 3 weeks ciprofloxacin / 3 months nebulised colistin course

- Admit for 2 weeks of IV antibiotics (tobramycin and ceftazidime)
- And either:
    - 3 further months nebulised Colomycin (1 mu bd)
      or
    - 3 further months of alternating nebulised Colomycin (1mu bd) / Tobramycin (300mg bd) / Colomycin (1mu bd) or Tobramycin (300mg bd) / Colomycin (1mu/bd) / Tobramycin (300mg bd)

N.B. If Tobramycin is used, either TOBI or Bramitob is acceptable

3d. Regrowth after IVs and at least 6 months of nebulised colistin

- Try 28 days nebulised TOBI ™ (Gibson et al. 841-49) and then continuous nebulised colistin 1 mu bd for a further six months. In practice this is unlikely to arise during the study

3e. Regrowth > 6 months from first growth

- Treat as for 3a ie first growth.

3f. Chronic Pseudomonas Infection

Defined for analysis purposes by the Leeds criteria:(Lee et al. 29-34)

Never	never cultured
Free	cultured previously but not in last year
Intermittent	cultured in < 50% of samples in past year
Chronic	cultured in > 50% of samples in past year

4. Staphylococcus aureus

4a. First growth

Well child (clinical judgment), home therapy:

- Oral Augmentin Duo (400/57) 0.3 mls/kg bd for 2 (minimum) to 4 weeks (clinical judgment)

- or equivalent dose of co-amoxiclav syrup **tds**
  0.25ml/kg TDS co-amoxiclav 250/62
  for 2 (minimum) to 4 weeks (clinical judgment)

Unwell child (clinical judgement), hospital therapy:
Tobramycin 10 mg/kg once daily (trough level 23 hours after 1st dose, must be < 1 mg/l), for 2 weeks, PLUS

- Teicoplanin 10 mg/kg 12 hrly for 3 doses then 10 mg/kg once daily for 2 weeks total

4b. Re-growth after more than 6 months from first growth

- Treat as for 4a ie first growth.

4c. Re-growth less than 6 months from first growth

- Oral flucloxacillin 50mg/kg bd for 28 days

4d. Further re-growth within 6 months

- Two oral anti-staphylococcal antibiotics (clinical judgment) for 28 days.

5. Haemophilus influenzae

5a. First growth

Well child (clinical judgement), home therapy:

- Oral Augmentin Duo (400/57) 0.3 mls/kg bd for 2 (minimum) to 4 weeks (clinical judgment)

- or equivalent dose of co-amoxiclav syrup **tds**
  0.25ml/kg TDS co-amoxiclav 250/62
  for 2 (minimum) to 4 weeks (clinical judgment)

Unwell child (clinical judgement), hospital therapy:

- IV tobramycin 10 mg/kg once daily for 2 weeks (trough level 23 hours after 1st dose, must be < 1 mg/l), PLUS
- IV ceftazidime 50 mg/kg three times a day

5b. Re-growth after more than 6 months from first growth

- Treat as for 5a ie first growth

5c. Re-growth less than 6 months from first growth

- Oral Augmentin Duo (400/57) 0.3 mls/kg bd for 2 (minimum) to 4 weeks (clinical judgment)
- or equivalent dose of co-amoxiclav syrup **tds**
  0.25ml/kg TDS co-amoxiclav 250/62

for 2 (minimum) to 4 weeks (clinical judgment)

5d. Further re-growth within 6 months

- Clarithromycin for 14-28 days.
  < 8kg: 7.5mg/kg bd
  8-11 kg: 62.5mg bd
  12-15kg 125 mg bd

In practice this is unlikely to arise during the study

6. Other growths

- Well child (clinical judgment), home therapy: Oral antibiotic (clinical judgment) for 2 (minimum) to 4 weeks

- Unwell child (clinical judgment), hospital therapy: 2 IV antibiotics (clinical judgment) for 2 weeks

7. Viral URTI (otherwise well child)

- Oral augmentin duo (400/57) 0.3 mls/kg bd for 2 (minimum) to 4 weeks (clinical judgment)

- or equivalent dose of co-amoxiclav syrup **tds**
  0.25ml/kg TDS co-amoxiclav 250/62
  for 2 (minimum) to 4 weeks (clinical judgment)

  Cough swab, treat as per protocol for any organism cultured.

8. Respiratory exacerbation with unknown organism, unwell child (clinical judgment)

Depending on severity of exacerbation:

- Oral augmentin duo (400/57) 0.3 mls/kg bd for 2 (minimum) to 4 weeks (clinical judgment)

- or equivalent dose of co-amoxiclav syrup **tds**
  0.25ml/kg TDS co-amoxiclav 250/62
  for 2 (minimum) to 4 weeks (clinical judgment)

  OR

- IV tobramycin 10 mg/kg once daily for 2 weeks (trough level 23 hours after 1st dose, must be < 1 mg/l), PLUS
- IV ceftazidime 50 mg/kg three times a day

Appendix IV - Social security benefits

1. Disability Living Allowance for children

DLA provides help with the extra costs of bringing up a child with disability. It is paid on top of any other income and also gives access to other kinds of help. There are two parts to DLA:

- **Care component** - for children needing a lot of extra personal care, supervision or watching over because of their condition. This is paid at 3 different rates. It can be paid from the age of 3 months, or from birth for a terminally ill baby.
- **Mobility component** - for children aged 3 or over who cannot walk or have walking difficulties or aged 5 or over who need extra guidance or supervision walking outdoors.

1) The care component

Your child can only qualify if they need more care or supervision than other children of the same age who are not disabled. The care component can be paid at one of three rates. The highest rate is paid if your child needs help throughout the day and throughout the night. The middle rate is paid if they need help throughout the day or throughout the night. The lowest rate is for a child if they need extra care for at least one hour per day.

2) The mobility component

The mobility component can be paid at two different rates, each of which has very different qualifying conditions.

The higher rate

1. that a child is unable to walk

2. that a child is virtually unable to walk

3. 'the exertion required to walk would constitute a danger to life or would be likely to lead to a serious deterioration in health'

The lower rate

This rate can only be paid for children who are at least 5 years old. It is for children who can walk but need extra guidance or supervision outdoors. The difficulties can be due to physical or mental health problems.

TIPS TO GIVE TO PARENTS

1. Don't lose benefit: the claim form will take some time to complete. Ensure the claim is lodged by phoning the Benefits Enquiry Line 08457 123456

2. Once at home, keep a diary of all the care given and time taken in connection with managing the child's condition. Include indirect and ancillary attention e.g. measuring doses, washing and drying and putting away of equipment.

3. Assume the person assessing the claim knows absolutely nothing about cystic fibrosis or children and is not a doctor.

4. Check out proposed answers with a professional familiar with daily care needs of a child with cystic fibrosis and if possible, with a local C.A.B or Welfare Rights Advisor.

5. Ask Cystic Fibrosis Trust for supporting letter.

6. Keep a photocopy of completed form.

Carer's Allowance

If a child receives either middle or higher rate of DLA care component either parent may claim Carers Allowance if he/she

- spends at least 35 hours per week caring for the child.
- passes U.K residence and presence tests.
- is not in full time education, is attending a course and/or having supervised study for 21 hours per week, not including meal breaks.
- if in work does not earn more than £100 per week once allowable expenses are deducted (these include tax, N.I, half of contribution to a pension scheme, some payments for child care to a person other than a close relative).

N.B Applying for benefits and appeals against decisions is complex and we recommend that families access appropriate specialist advice.

3. The Family Fund

The Family Fund is funded by the Government to help families with severely disabled or seriously ill children. The Family Fund works within guidelines agreed by the trustees. These are concerned with the child's disability or illness, the family's financial circumstances and the kind of help given. The Family Fund cannot usually help if a family's income is more than £25,000 gross p.a. (figure June 2010). Disability Living Allowance and Child Benefit are not counted as income.

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Appendix V –Tables for body surface area

BODY SURFACE AREA IN CHILDREN

Body-weight under 40kg

Body-weight (kg)	Surface area (m^2)
1	0.10
1.5	0.13
2	0.16
2.5	0.19
3	0.21
3.5	0.24
4	0.26
4.5	0.28
5	0.30
5.5	0.32
6	0.34
6.5	0.36
7	0.38
7.5	0.40
8	0.42
8.5	0.44
9	0.46
9.5	0.47
10	0.49
11	0.53
12	0.56
13	0.59
14	0.62
15	0.65
16	0.68

Body-weight (kg)	Surface area (m^2)
17	0.71
18	0.74
19	0.77
20	0.79
21	0.82
22	0.85
23	0.87
24	0.90
25	0.92
26	0.95
27	0.97
28	1.0
29	1.0
30	1.1
31	1.1
32	1.1
33	1.1
34	1.1
35	1.2
36	1.2
37	1.2
38	1.2
39	1.3
40	1.3

Values are calculated using the Boyd equation

Note Height is not required to estimate body surface area using these tables

BODY SURFACE AREA IN CHILDREN

Body-weight over 40kg

Body-weight (kg)	Surface area (m^2)
41	1.3
42	1.3
43	1.3
44	1.4
45	1.4
46	1.4
47	1.4
48	1.4
49	1.5
50	1.5
51	1.5
52	1.5
53	1.5
54	1.6
55	1.6
56	1.6
57	1.6
58	1.6
59	1.7
60	1.7
61	1.7
62	1.7
63	1.7
64	1.7
65	1.8

Body-weight (kg)	Surface area (m^2)
66	1.8
67	1.8
68	1.8
69	1.8
70	1.9
71	1.9
72	1.9
73	1.9
74	1.9
75	1.9
76	2.0
77	2.0
78	2.0
79	2.0
80	2.0
81	2.0
82	2.1
83	2.1
84	2.1
85	2.1
86	2.1
87	2.1
88	2.2
89	2.2
90	2.2

Values are calculated using the Boyd equation

Note Height is not required to estimate body surface area using these tables

Appendix VI - SHO competency assessment for percutaneous longline insertion

(this must be completed before SHO is allowed to insert PICC)

NAME:…….

DATE OF ASSESSMENT:…….

UNDERSTANDS INDICTATION FOR INSERTION □

UNDERSTANDS POTENTIAL COMPLICATIONS □

CHOOSES SUITABLE SITES FOR INSERTION □

FAMILIAR WITH LONGLINE KIT AND INSERTION TECHNIQUE □

FAMILIAR WITH ASEPTIC TECHNIQUE □

PRACTICED PROCEDURE ON OPEN KIT □

Name of assessor: (SpR)……..

Signature of assessor:……

Signature of SHO:…….

Appendix VII - GP Shared care documents: Pulmozyme (DNase)

Template developed and approved by NWL Medicines Management Pharmacy Network Dec 2003

(Sharing Organisations: Royal Brompton & Harefield NHS Trust & Kensington & Chelsea PCT)

SHARED CARE DOCUMENT

Recombinant Human Dornase alfa - (Pulmozyme)

Adult & Paediatric Patients

CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP agree that the patient's condition is appropriate.
- The patient will only be referred to the GP once the GP has agreed in each individual case, and the hospital will continue to provide prescriptions until there has been successful transfer of the responsibilities outlined below.
- The patient will be commenced and stabilized on Dornase alfa before referral to the GP for shared care. A **minimum** period of **ONE month** stabilization is necessary before shared care arrangements are commenced.

NOTES to the GP

Are you confident that you can take on the clinical responsibility of prescribing this drug?

The questions below will help you answer this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care document?
- Have you been provided with relevant clinical details including monitoring data?
- Have this document and BNF provided sufficient information for you to feel confident in accepting clinical and legal responsibility for prescribing?

If, after reading the shared care document, you can answer YES to all these questions, then it is appropriate for you to accept prescribing responsibility.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing.

GP agreement is voluntary; with the right to decline to share care if for any reason you do not feel confident in accepting clinical responsibility. Refusal should not be for financial reasons and the cost of the drug is NOT a barrier to sharing care. All prescribers will want to keep reasonably up-to-date with important developments in therapeutics. Practitioners have a duty to keep themselves informed of the drugs that are recommended for their patients.

Your PCT pharmacist will support you when making decisions about shared care

Date prepared: November 2005 **Updated: April 2009** **Review Date: April 2011**	**Prepared by:** Mami Harrison, Specialist Pharmacist, Respiratory Medicine **Approved by:** **Royal Brompton & Harefield Trust** Prof. Margaret Hodson, Dr Khin Gyi and Dr Diana Bilton, Consultant Physicians, Respiratory Medicine Prof. Andrew Bush, Dr Mark Rosenthal, Dr Ian Balfour-Lynn and Dr Jane Davies, Consultant Physicians, Paediatrics Drugs & Therapeutics committee. **Kensington & Chelsea PCT** Anne-Marie McCooey, Medicines Management Pharmacist

Recombinant Human Dornase alfa (Pulmozyme)

BACKGROUND INFORMATION

Patients with Cystic Fibrosis have thick tenacious sputum, the retention of which contributes to infective exacerbations and reduced pulmonary function. The thick secretions contain a high concentration of extracellular DNA released by degenerating leukocytes, which accumulate in response to infection and add to the viscosity of the secretions. Thick secretions lead to mucus plugging of the airways and further cycles of infection and inflammation.

Dornase alfa (DNase) is a genetically engineered version of a naturally occurring enzyme, which cleaves extracellular DNA in the sputum and therefore reduces its viscosity and aids sputum removal.

1. Areas of responsibility

Consultant	GP
1. Assess suitability of patients for treatment. 2. **Ideally** commence patient on a trial of dornase alfa when the patient's condition is stable. However, there may be instances where patients are initiated on therapy when they are not stable i.e. during an exacerbation and sputum retention is problematic. Prior to starting therapy the patient' s lung function, weight, oxygen saturation and symptoms will be assessed and recorded in the patient's clinical notes. 3. Initiate and supply the 1st month of treatment, and where necessary refer the patient to the physiotherapist to obtain a suitable nebuliser and compressor. 4. Send GP a letter informing them that the patient is being assessed for dornase alfa therapy, along with a copy of these guidelines, the dornase alfa patient information leaflet, 2 published articles and Summary of product characteristics (see specialist support etc. p3) and ask the GP if they are willing to prescribe	1. Monitor the patients overall health, well being and changes in respiratory symptoms (e.g. increased shortness of breath, increased cough, change in sputum production and reduction in exercise tolerance) 2. Prescribe continuing dornase alfa therapy after 6 weeks. If there is a problem with prescribing continuing care, then the patient's consultant must be informed within 2 weeks of the patient's dornase alfa therapy being initiated. 3. Liaise with the patient's consultant regarding any complications or adverse effects of treatment. 4. If the GP would like to, and is able to do so then monitor the patient's peak flow or FEV_1. Any concerns should be highlighted and discussed with the patient's consultant (such as a drop in FEV_1 of 10% or more). 5. In the event of a minor infection then treatment with oral antibiotics should be initiated. In the event of a severe infective exacerbation the Cystic fibrosis registrar or consultant should be contacted, and the patient referred to hospital. Dornase alfa therapy should not be altered or stopped in the event of an infection.

5. Assess and monitor patient's response to therapy after 1 month. If a positive response is obtained demonstrated by an improvement in any of the following: lung function ie. usually an increase of ≥5% in FEV1, symptoms, exercise tolerance, sputum clearance and well being, the patient will be given a further 2 weeks supply of dornase alfa. If the GP has agreed to prescribe dornase alfa, the patient will then be advised to obtain continuing supplies from their GP. 6. Send GP a second letter informing them of the outcome of the trial, as well as the patient's lung function results. 7. Monitor patients continuing response as stated above in clinic on a 3 monthly basis, and send a letter to the GP following clinic. 8. Institute changes in therapy ie. alter the patient's dose where appropriate, and inform the GP of any changes. If the dose is changed to an unlicensed dose, the GP will be informed of this. 9. Provide information and support to the GP.	

2. **COMMUNICATION AND SUPPORT**

Hospital contacts:	**Out of hours contacts & procedures:**
(the referral letter will indicate named consultant) Royal Brompton & Harefield NHS Trust **Consultants:** **Adults:** Prof. Margaret Hodson, Dr. Khin Gyi and Dr. Diana Bilton **Paediatrics**: Prof. Andrew Bush, Dr. Mark Rosenthal, Dr. Ian Balfour-Lynn and Dr Jane Davies **Pharmacy Medicines Information:** 020 7351 8901 **Physiotherapy Department** (for equipment queries or problems): 0207 351 8088 Tel: 0207 352 8121 *switchboard* (or as indicated on the referral letter) Fax: as indicated on the referral letter E-mail: as indicated on the referral letter	Contact the on call adult or paediatric Specialist Registrar via switchboard on: 020 7352 8121 Contact the on call physiotherapist for any equipment queries or problems via switchboard on: 020 7352 8121

Specialist support/resources available to GP including patient information:

1. Shah P.L, Hodson M.E,
Dornase Alfa, A practical guide to patient selection and drug use in cystic fibrosis,
BioDrugs 1997 Dec:8(6):439-445.
2. Hodson M.E, McKenzie S et al.,
Dornase Alfa in the treatment of cystic fibrosis in Europe: A report from the epidemiologic registry of cystic fibrosis,
Paediatric Pulmonolgy 36:427-432, 2003.
3. Clinical Guidelines: Care of Children with Cystic Fibrosis 2007. Available at: www.rbht.nhs.uk/childrencf
4. Dornase Alfa (Pulmozyme) patient information leaflet, May 2006.
5. Suri R, Metcafe C et al.
Comparison of hypertonic saline and alternate day or daily recombinant human deoxyribonuclease (DNase) in children with cystic fibrosis: a randomised trial. Lancet 2001: 358(9290);1316-1321

3. CLINICAL INFORMATION

See the BNF and Summary of Product Characteristics (SPC) for Dornase alfa (Pulmozyme) for further information

Indication(s) for this agreement:	• Reduction of mucus viscosity and increase in clearance of airway secretions in cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted, aged 5 years and above to improve pulmonary function. • In exceptional circumstances, some children under the age of 5 who suffer from the following may be initiated on dornase alfa (unlicensed): - Multiple exacerbations requiring courses of intravenous antibiotics - 1 severe or >1 mild episode of segmental or lobar atelectasis - Difficult to clear viscous secretions - Impaired quality of life ⁕ The European Cystic Fibrosis Society Consensus report due to be published at the end of this year, is expected to recommend that dornase alfa be given to all children aged 6 years and above.
Dose	• The recommended dose is 2.5mg (2,500 units) once daily, but some patients over the age of 21 may benefit from twice daily dosing. Although unlicensed there is data to show that dornase alfa can safely and effectively be used twice daily in patients under the age of 21 (communication from Roche) • There are some patients whose dose may be decreased to 2.5mg on alternate days, depending on their response to therapy (unlicensed[5]). Any dose changes will be made by the Cystic fibrosis team and communicated to the GP.
Intended duration of treatment:	• For as long as the patient's consultant considers the patient is gaining clinical benefit from therapy with dornase alfa
Contraindications	• Hypersensitivity to the active ingredient or its excipients.
Cautions	• The safety of dornase alfa has not been established in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, or embryofoetal development (see section. Caution should be exercised when prescribing dornase alfa to pregnant women. • As it is not known whether dornase alfa is excreted in human milk, caution should be exercised when dornase alfa is administered to a breast-feeding woman
Summary of adverse effects: (See summary of product characteristics (SmPC) for full list)	• Few patients have experienced adverse effects that have required permanent discontinuation of dornase alfa. Adverse effects are rare (<1/1000), in most cases the effects are mild and transient in nature, and do not require alterations in dornase alfa dosing. • Vocal effects: Voice alteration, pharyngitis, laryngitis, dyspnoea, rhinitis • Pulmonary function: Upon initiation of therapy a transient decline in pulmonary function may occur. • Skin & appendages: Rash & urticaria • Special senses: Conjunctivitis • Body as a whole: Chest pain, fever • Gastrointestinal: Dyspepsia • If the patient suffers from any adverse effects, this should be discussed with the Cystic Fibrosis Team
Monitoring that should be undertaken by the GP (what and when):	o See section 1. o No documented clinically significant drug interactions. Dornase alfa can be given safely & effectively with standard cystic fibrosis medicines.

Practical issues:	• Dornase alfa should not be diluted or mixed with any other drug • It should be stored in a fridge (2°C - 8°C) • Dornase alfa should be protected from strong light • TOBI should be inhaled using a suitable nebuliser such as the Pari LC Plus, Pari E-flow device and INEB, the use of which has been confirmed by the manufacturers. Ultrasonic nebulisers should not be used as Dornase alfa maybe inactivated. • Avoid exposure to excessive heat. A single brief exposure to elevated temperatures (≤ 24 hours up to a maximum of 30°C) does not affect product stability.

4. GENERAL INFORMATION

Patients are issued with the nebuliser, air compressor and necessary nebuliser accessories by the Trust's physiotherapy department. All of the equipment and accessories are brought back to physiotherapy annually for a service check, and the air inlet filter of the compressor and nebuliser parts replaced.

Patients are issued with an information sheet on the general maintenance and cleaning of their equipment by the physiotherapy department.

Appendix VIII - GP Shared care documents: Bramitob / TOBI

(Sharing Organisations: Royal Brompton & Harefield NHS Trust & Kensington & Chelsea PCT)

SHARED CARE DOCUMENT

Tobramycin 300mg nebuliser solution (BRAMITOB/TOBI)

Adult & Paediatric Patients

CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP agree that the patient's condition is appropriate.
- The patient will only be referred to the GP once the GP has agreed in each individual case, and the hospital will continue to provide prescriptions until there has been successful transfer of the responsibilities outlined below.
- The patient will be commenced and stabilized on tobramycin nebuliser solution before referral to the GP for shared care. A **minimum** period of **ONE month** stabilisation is necessary before shared care arrangements are commenced.

NOTES to the GP

Are you confident that you can take on the clinical responsibility of prescribing this drug?

The questions below will help you answer this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care document?
- Have you been provided with relevant clinical details including monitoring data?
- Have this document and BNF provided sufficient information for you to feel confident in accepting clinical and legal responsibility for prescribing?

If, after reading the shared care document, you can answer YES to all these questions, then it is appropriate for you to accept prescribing responsibility.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing.

GP agreement is voluntary; with the right to decline to share care if for any reason you do not feel confident in accepting clinical responsibility. Refusal should not be for financial reasons and the cost of the drug is NOT a barrier to sharing care. All prescribers will want to keep reasonably up-to-date with important developments in therapeutics. Practitioners have a duty to keep themselves informed of the drugs that are recommended for their patients.

Your PCT pharmacist will support you when making decisions about shared care

Date prepared: November 2008 **Date updated**: April 2009 **Review date:** April 2011	**Prepared by:** Mami Harrison, Specialist Pharmacist, Respiratory Medicine **Approved by:** Prof. Margaret Hodson, Dr Khin Gyi & Dr Diana Bilton, Consultant Physicians, Respiratory Medicine Prof. Andrew Bush, Dr Mark Rosenthal, Dr Ian Balfour-Lynn, Dr Jane Davies, Consultant Physicians, Paediatrics **Kensington & Chelsea PCT** Anne-Marie McCooey, Medicines Management Pharmacist

Tobramycin 300mg nebuliser solution (BRAMITOB/TOBI)

BACKGROUND INFORMATION

Lung damage associated with persistent infection by *Pseudomonas aeruginosa* is a major cause of morbidity and mortality in patients with Cystic Fibrosis (CF). Treatment with nebulised tobramycin in patients chronically colonised with *Pseudomonas aeruginosa* has been shown to improve lung function, decrease sputum pseudomonas density, and to reduce the frequency of hospital admissions and the need for intravenous anti-pseudomonal antibiotics.
BRAMITOB and TOBI are preservative free solutions of tobramycin, which are licensed for nebulisation in patients with cystic fibrosis.

1. AREAS OF RESPONSIBILITY

Consultant *(include follow up and monitoring arrangements, details to provide to GP, communication with GP, provision of patient information)*	**GP** (*include monitoring arrangements and indicate when and how to refer back to consultant)*
1. Assess suitability of patient for treatment. 2. Prior to starting therapy the patient's lung Function (when old enough to perform), weight, oxygen saturation, renal function and symptoms will be assessed and recorded in the patient's clinical notes. 3. Refer the patient to the physiotherapist for a bronchoconstriction trial, where the patient's first dose will be supervised. Spirometry will be performed prior to and post the first dose to check for bronchoconstriction. If required the patient will be provided with a suitable nebuliser and compressor by the physiotherapist. 4. Initiate and supply the 1st month of treatment. 5. Send the GP a letter informing them that their patient has been started on nebulised BRAMITOB/TOBI, along with a copy of these guidelines, BRAMITOB/TOBI patient information leaflet, Summary of product characteristics and published article (see specialist support etc. p3), and ask the GP if they are willing to prescribe. 6. Assess and monitor patient's response to therapy after 1 month and then 3 monthly thereafter, and provide the GP with a written summary. The patient's response to therapy will be assessed by monitoring their lung function, a reduction in exacerbation rates and need for treatment with intravenous anti-pseudomonal	1. Monitor the patients overall health, well being and changes in respiratory symptoms (e.g. increased shortness of breath, increased cough, change in sputum production and reduction in exercise tolerance) 2. Prescribe continuing TOBI therapy after the patient's initial month of therapy (ie. month 3). If there is a problem with prescribing continuing care, the patient's consultant must be informed as soon as possible. 3. Liaise with the patient's consultant regarding any complications or adverse effects of treatment. 4. Inform the patient's consultant if there is any deterioration in the patient's condition during their month off TOBI. 5. In the event of a minor infection then treatment with oral antibiotics should be initiated. In the event of a severe infective exacerbation the Cystic fibrosis registrar or consultant should be contacted, and the patient referred to hospital. TOBI therapy should not be altered or stopped in the event of an infection.

antibiotics, improvement in subjective symptoms and improvement in the patient's general well being. On the rare occasion where TOBI is used for eradication therapy, the patient's response will be assessed on the outcome of respiratory cultures, and whether the culture is positive or negative for *Pseudomonas aeruginosa* after 28 days. 7. The GP will be sent a letter following the patient's 1 month review, and if the GP has agreed to prescribe the patient will be advised to obtain ongoing therapy from their GP. 8. Monitor patients continuing response as described above 3 monthly and renal function annually, and provide a written summary to the GP. 9. Provide information and support to the GP.	

Tobramycin 300mg nebuliser solution (BRAMITOB/TOBI)

2. COMMUNICATION AND SUPPORT

Hospital contacts:	**Out of hours contacts & procedures:**
(the referral letter will indicate named consultant) **Royal Brompton & Harefield NHS Trust** **Consultants:** **Adults:** Prof. Margaret Hodson, Dr Khin Gyi and Dr Diana Bilton **Paediatrics**: Prof. Andrew Bush, Dr. Mark Rosenthal, Dr. Ian Balfour-Lynn and Dr Jane Davies Tel: 020 7352 8121 *switchboard* (or as indicated on the referral letter) Fax: as indicated on the referral letter E-mail: as indicated on the referral letter **Physiotherapy Department** (for equipment queries or problems): 020 7351 8088 **Pharmacy Medicines Information:** 020 7351 8901	Contact the on call Respiratory adult or paediatric Registrar via switchboard on: 020 7352 8121 Contact the on call physiotherapist for any equipment queries or problems via switchboard on: 020 7352 8121
Specialist support/resources available to GP including patient information:	

1. Ramsey B., Pepe M., Quan J., et al.
Intermittent Administration of Inhaled Tobramycin in Patients with Cystic Fibrosis,
NEJM, Vol.340; Jan 7th 1999; p23-30
2. TOBI Patient information leaflet, 2006
3. TOBI SPC, September 2006
4. Clinical Guidelines: Care of Children with Cystic Fibrosis 2007. Available at: www.rbht.nhs.uk/childrencf
5. Antibiotic treatment for Cystic Fibrosis, Cystic Fibrosis Trust, September 2002.
Available at: www.cftrust.org.uk

3. CLINICAL INFORMATION

See the BNF and Summary of Product Characteristics for TOBI for further information

Indication(s) for this agreement:	• TOBI is prescribed for the following 2 indications: 1) Long-term management of chronic *Pseudomonas aeruginosa* infections of the lungs in patients with cystic fibrosis 2) On rare occasions for the eradication of *Pseudomonas Aeruginosa* in patients in whom 1st line treatment with colistin and ciprofloxacin have failed or are not tolerated. It is given for a duration of 28 days (unlicensed use). • Within the Trust TOBI is used second line for the long term management of chronic *Pseudomonas aeruginosa* infections of the lungs. • For long term therapy it is prescribed in patients who are currently receiving nebulised Colistin but who continue to deteriorate on colistin, or in patients who are unable to tolerate colistin due to significant bronchoconstriction. • It is not used as an alternative to intravenous or appropriate oral antibiotics for the treatment of acute exacerbations.
Dose	• The recommended dose for adults and children is 300mg (contents of one ampoule) nebulised twice a day for 28 days, followed by a therapy free interval of 28 days. • A cycle of 28 days of active therapy and 28 days off treatment should be maintained thereafter. • TOBI may be prescribed on an alternate month basis as the sole nebulised antibiotic in patients chronically infected with *Pseudomonas Aeruginosa.* However, it may also be prescribed on an alternate month basis, alternating with nebulised colistin during the non-TOBI month, in patients who clinically decline during the non-TOBI month. • The dose is not adjusted for weight, and therefore all patients should receive 300mg twice daily. • Before TOBI is started a nebulised trial of 300mg must be carried out by the physiotherapist to ensure that the patient does not experience any problems such as bronchoconstriction, an inhaled or nebulised bronchodilator such as salbutamol should be given beforehand if this is part of the patient's current regimen. • If there is evidence of therapy induced bronchoconstriction in a patient not receiving a bronchodilator, the trial may be repeated at another time (at least 12 hours after the first dose) with a bronchodilator such as salbutamol being used beforehand.
Intended duration of treatment:	• For as long as the patient's consultant considers the patient is gaining clinical benefit from the inclusion of TOBI in their treatment regimen.
Contraindications	• Hypersensitivity to any aminoglycoside
Cautions	• TOBI should be used with caution in patients with known or suspected

	renal, auditory, vestibular or neuromuscular disorders such as parkinsonism, myasthenia gravis or with severe active haemoptysis. • There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Animal studies do not indicate a teratogenic effect of tobramycin, however, aminoglycosides can cause foetal harm (e.g. congenital deafness) when high systemic concentrations are achieved in pregnant women. If TOBI is used during pregnancy, or if the patient becomes pregnant while taking TOBI, they should be informed of the potential hazard to the foetus. TOBI should only be initiated on consultant decision following discussion with the patient. • Systemic tobramycin is excreted in breast milk. It is not known if administration of TOBI will result in serum concentrations high enough for tobramycin to be detected in breast milk. Because of the potential for ototoxicity and nephrotoxicity with tobramycin in infants, a decision should be made whether to terminate nursing or discontinue TOBI therapy
Summary of adverse effects: (See summary of product characteristics (SmPC) for full list)	• TOBI was well tolerated in placebo controlled clinical trials, with voice alterations (hoarseness) and tinnitus being reported by a larger number of patients treated with TOBI (13% TOBI vs 7% control). These episodes of tinnitus were transient and resolved without discontinuation of TOBI therapy, and were not associated with permanent loss of hearing on audiogram testing. The risk of tinnitus did not increase with repeated cycles of exposure to TOBI. • Other adverse effects include increased cough, pharyngitis, rhinitis, headache, haemoptysis, bronchospasm, voice alteration, increased sputum, chest pain, mouth ulceration, nausea and vomiting. • If the patient suffers from any adverse effects, this should be discussed with the Cystic Fibrosis Team
Monitoring that should be undertaken by the GP (what and when):	• See section 1. • Concurrent and/or sequential use of TOBI with other medicinal products with nephrotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. TOBI should not be administered concomitantly with furosemide, urea or mannitol.
Administration/Practical issues:	• TOBI should be inhaled using the PARI LC PLUS or another suitable nebuliser such as the INEB and E-flow device, the use of which has been confirmed by the manufacturers. • It should not be diluted or mixed with any other drug. • Where patients are receiving several inhaled therapies TOBI should be nebulised last. • TOBI must be stored in a refrigerator at 2-8 °C in its original container. • TOBI is sensitive to intense light. • The solution is normally slightly yellow in colour.

4. GENERAL INFORMATION

Patients are issued with the nebuliser, air compressor and necessary nebuliser accessories by the Trust's physiotherapy department. All of the equipment and accessories are brought back to physiotherapy annually for a service check, and the air inlet filter of the compressor and nebuliser parts replaced.
Patients are issued with an information leaflet on the general maintenance and cleaning of their equipment by the physiotherapy department.

Appendix IX - GP Shared care documents: Colomycin

(Sharing Organisations: Royal Brompton & Harefield NHS Trust & Kensington & Chelsea PCT)

SHARED CARE DOCUMENT

Colistin 500,000, 1 million or 2 million International Units (MU) (Colomycin injection administered by inhalation)

CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP agree that the patient's condition is appropriate.
- The patient will only be referred to the GP once the GP has agreed in each individual case, and the hospital will continue to provide prescriptions until there has been successful transfer of the responsibilities outlined below.
- The patient will be commenced and stabilized on **Colistin** before referral to the GP for shared care. A **minimum** period of **ONE month** stabilization is necessary before shared care arrangements are commenced.

NOTES to the GP

Are you confident that you can take on the clinical responsibility of prescribing this drug?

The questions below will help you answer this:

- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care document?
- Have you been provided with relevant clinical details including monitoring data?
- Have this document and BNF provided sufficient information for you to feel confident in accepting clinical and legal responsibility for prescribing?

If, after reading the shared care document, you can answer YES to all these questions, then it is appropriate for you to accept prescribing responsibility.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should write to the consultant within 14 days, outlining your reasons for NOT prescribing.

GP agreement is voluntary; with the right to decline to share care if for any reason you do not feel confident in accepting clinical responsibility. Refusal should not be for financial reasons and the cost of the drug is NOT a barrier to sharing care. All prescribers will want to keep reasonably up-to-date with important developments in therapeutics. Practitioners have a duty to keep themselves informed of the drugs that are recommended for their patients.

Your PCT pharmacist will support you when making decisions about shared care

Date prepared: November 2008 **Date updated**: April 2009 **Review date:** April 2011	**Prepared by:** Mami Harrison, Specialist Pharmacist, Respiratory Medicine **Approved by:** Prof. Margaret Hodson, Dr Khin Gyi & Dr Diana Bilton, Consultant Physicians, Respiratory Medicine Prof. Andrew Bush, Dr Mark Rosenthal, Dr Ian Balfour-Lynn, Dr Jane Davies, Consultant Physicians, Paediatrics **Kensington & Chelsea PCT** Anne-Marie McCooey, Medicines Management Pharmacist

Colistin 500,000 units, 1 million or 2 million international units (MU) (Colomycin injection administered by inhalation)

BACKGROUND INFORMATION

Lung damage associated with persistent infection by *Pseudomonas aeruginosa* is a major cause of morbidity and mortality in patients with Cystic Fibrosis (CF). Treatment with nebulised anti-pseudomonal antibiotics in patients chronically colonised with *Pseudomonas aeruginosa* has been shown to improve lung function, decrease sputum pseudomonas density, reduce the frequency of infective exacerbations and the need for intravenous anti-pseudomonal antibiotics. Colistin is a polymyxin antibiotic, which is licensed for nebulisation in patients with cystic fibrosis.

1. AREAS OF RESPONSIBILITY

Consultant *(include follow up and monitoring arrangements, details to provide to GP, communication with GP, provision of patient information)*	**GP** *(include monitoring arrangements and indicate when and how to refer back to consultant)*
1. Assess suitability of patient for treatment. For the eradication of Pseudomonas aeruginosa following the first or new isolation, all patients will be initiated on nebulised colistin unless they are unable to tolerate it. 2. Prior to starting therapy the patient's lung function (when old enough to perform), weight, oxygen saturation and symptoms will be assessed and recorded in the patient's clinical notes. 3. Refer the patient to the physiotherapist for a bronchoconstriction trial, where the patient's first dose will be supervised. Spirometry will be performed prior to and post the first dose to check for bronchoconstriction. If required the patient will be provided with a suitable nebuliser and compressor by the physiotherapist. 4. Initiate and supply the 1st month of treatment. 5. Send the GP a letter informing them that their patient has been started on nebulised colistin for either eradication or long term therapy, along with a copy of these guidelines, colistin summary of product characteristics and colistin patient information leaflet (see specialist support etc. p3), and the GP asked to take on the prescribing of colistin.	1. Monitor the patients overall health, well being and changes in respiratory symptoms (e.g. increased shortness of breath, increased cough, change in sputum production and reduction in exercise tolerance) 2. Prescribe continuing colistin therapy after the patient's initial month of therapy (i.e. month 2). 3. If there is a problem with prescribing continuing care, the patient's consultant must be informed within 2 weeks of the patient's colistin therapy being initiated. 4. Liaise with the patient's consultant regarding any complications or adverse effects of treatment. 5. Inform the patient's consultant if there is any deterioration in the patient's condition. 6. In the event of a minor infection then treatment with oral antibiotics should be initiated. In the event of a severe infective exacerbation the Cystic fibrosis registrar or consultant should be contacted, and the patient referred to hospital. Colistin therapy should not be altered or stopped in the event of an infection.

6. Assess and monitor patients response to therapy on a 3 monthly basis, and the GP provided with a written summary. For patient's on long-term therapy the patient's response to therapy will be assessed by monitoring their lung function, a reduction in exacerbation rates and need for treatment with intravenous anti-pseudomonal antibiotics, improvement in subjective symptoms and improvement in the patient's general well being. For patients on eradication therapy response will be assessed on the outcome of respiratory cultures, and whether the culture is positive or negative for *Pseudomonas aeruginosa*. 7. Provide information and support to the GP.	

Colistin 500,000 units, 1 million or 2 million international units (MU) (Colomycin injection administered by inhalation)

2. COMMUNICATION AND SUPPORT

Hospital contacts:	**Out of hours contacts & procedures:**
(the referral letter will indicate named consultant) **Royal Brompton & Harefield NHS Trust** **Consultants:** **Adults:** Prof. Margaret Hodson, Dr Khin Gyi and Dr Diana Bilton **Paediatrics**: Prof. Andrew Bush, Dr. Mark Rosenthal, Dr. Ian Balfour-Lynn and Dr Jane Davies Tel: 020 7352 8121 *switchboard* (or as indicated on the referral letter) Fax: as indicated on the referral letter E-mail: as indicated on the referral letter **Physiotherapy Department** (for equipment queries or problems): 020 7351 8088 **Pharmacy Medicines Information:** 020 7351 8901	Contact the on call Respiratory adult or paediatric Registrar via switchboard on: 020 7352 8121 Contact the on call physiotherapist for any equipment queries or problems via switchboard on: 020 7352 8121

Specialist support / resources available to GP including patient information:

1. Colistin Summary of Product Characteristics October 2008, Forest Laboratories UK Limited.
2. Colistin patient information leaflet, November 2004
3. Clinical Guidelines: Care of Children with Cystic Fibrosis 2007. Available at: www.rbht.nhs.uk/childrencf
4. Antibiotic treatment for Cystic Fibrosis, Cystic Fibrosis Trust, September 2002. Available at: www.cftrust.org.uk

3. CLINICAL INFORMATION

See the BNF and Summary of Product Characteristics (SPC) for Colomycin injection for further information

Indication(s) for this agreement:	• Colistin is indicated for both: - Eradication of first or new isolate of *pseudomonas aeruginosa* for a treatment duration of usually 3 months and - Long-term management of chronic *Pseudomonas aeruginosa* infections of the lungs. • Nebulised Colistin is not used as an alternative to intravenous or appropriate oral antibiotics for the treatment of acute exacerbations. • Within the Trust Colistin is used **First Line** for both of the above indications.
Dose	• The SPC recommends the following doses for guidance: Children <2 years: 500,000-1 million units twice daily Children>2 years and adults: 1-2 million units twice daily • However, locally we use the following doses: For Paediatric patients: <2yrs: 250,000 units twice daily 2-8yrs: 500,000-1 million units twice daily >8yrs: 1-2 million units twice daily For adult patients the dose is 1-2 million units twice daily • The decision to increase the patient's dose will be made by the cystic fibrosis team according to the patient's response, if it is felt that the patient would benefit form a higher dose. In the case of children the dose will be increased with increasing age. Any change in dose will be made during the patient's inpatient stay or outpatient clinic, and any change communicated to the GP. • Before colistin is started a nebulised trial must be carried out by the physiotherapist to ensure that the patient does not experience any problems such as bronchoconstriction, an inhaled or nebulised a short acting ß2 agonist such as salbutamol should be given beforehand if this is part of the patient's current regimen. • If there is evidence of therapy induced bronchoconstriction in a patient not receiving a bronchodilator, the trial may be repeated at another time (at least 12 hours after the first dose) with a short acting ß2 agonist being used beforehand.
Intended duration of treatment:	• For as long as the patient's consultant considers the patient is gaining clinical benefit from the inclusion of Colistin in their treatment regimen.
Contraindications	• Hypersensitivity to Colistin or to polymyxin B • Myasthenia gravis
Cautions	• Colistin should be used with caution in patients with renal impairment and porphyria • Safety in human pregnancy has not been established. There is evidence that colistimethate sodium crosses the placenta and consequently there is potential for foetal toxicity if administered during pregnancy. Animal studies are insufficient with respect to effects on reproduction. Colistin should only be given during pregnancy if the benefits outweigh any potential risk. The decision should be made by the consultant on discussion with the patient. • Colistin should be administered to breastfeeding women only when clearly needed.

Summary of adverse effects: (See summary of product characteristics (SmPC) for full list)	• Colistin may cause cough, bronchoconstriction, sore mouth or throat and thrush infections of the mouth or throat. Skin rash may also indicate hypersensitivity, if this occurs treatment should be withdrawn. • If the patient suffers from any adverse effects, this should be discussed with the Cystic Fibrosis Team
Monitoring that should be undertaken by the GP (what and when):	• See section 1. • Concomitant use with other medicinal products of neurotoxic and/or nephrotoxic potential should be avoided. Neuromuscular blocking drugs should be used with extreme caution. The risk of nephrotoxicity may be increased if given concomitantly with cephalosporin antibiotics.
Administration/Practical issues:	• The required amount of powder is dissolved in 2-4ml of water for injection or sodium chloride 0.9% as directed by the hospital • Colistin should be nebulised using a jet nebuliser. • Where patients are receiving several inhaled therapies, colistin should be nebulised last. • Colistin should not be stored above 25°C. • The vials must be stored in the outer carton to protect them form light**.**

4. GENERAL INFORMATION

Patients are issued with the nebuliser, air compressor and necessary nebuliser accessories by the Trust's physiotherapy department. All of the equipment and accessories are brought back to physiotherapy annually for a service check, and the air inlet filter of the compressor and nebuliser parts replaced.
Patients are issued with an information leaflet on the general maintenance and cleaning of their equipment by the physiotherapy department.

Appendix X – Travel letters

Date:

TO WHOM IT MAY CONCERN

Dear Sir/Madam,

Re:

The above mentioned child has cystic fibrosis and is currently under my care at the Royal Brompton Hospital. It is therefore necessary that the family carries with them on holiday the child's medications and these may include needles, syringes and a nebuliser device.

If any further information is required, please do not hesitate to contact my department at the Royal Brompton Hospital.

Yours faithfully,

PRINT NAME:

Signed:

Date:

TO WHOM IT MAY CONCERN

Dear Sir/Madam,

Re:

This child has cystic fibrosis.

When the patient named above was examined, he/she was fit to travel and I do not foresee any problems with his/her health whilst abroad.

Yours faithfully,

PRINT NAME:

Signed:

Appendix XI – Gene mutation nomenclature

DNA sequence change	Amino acid change	Commonly used nomenclature
c.254G>A	p.Gly85Glu	G85E
c.350G>A	p.Arg117His	R117H
c.443T>C[†]	p.Ile148Thr	I148T
c.489+1G>T (AJ574942.1:g.240G>T)		621+1G>T
c.579+1G>T (AJ574943.1:g.261G>T)		711+1G>T
c.948delT[†]	p.Phe316LeufsX12	1078delT
c.1000C>T	p.Arg334Trp	R334W
c.1040G>C	p.Arg347Pro	R347P
c.1210–12T(5_9) (AJ574948.1:g.152T (5_9))		5T/7T/9T polymorphism
c.1210–12[5][‡] (AJ574948.1:g.152T[5][‡])		5T
c.1210–12T[9][‡] (AJ574948.1:g.152T[9][‡])		9T
c.1364C>A	p.Ala455Glu	A455E
c.1519_1521delATC	p.Ile507del	Delta I507
c.1521_1523delCTT	p.Phe508del	Delta F508
c.1585–1G>A (AJ574980.1:g.116G>A)		1717–1G>A
c.1624G>T	p.Gly542X	G542X
c.1652G>A	p.Gly551Asp	G551D
c.1657C>T	p.Arg553X	R553X
c.1679G>C	p.Arg560Thr	R560T
c.1766+1G>A (AJ574983.1:g.179G>A)		1898+1G>A
c.2052delA	p.Lys684AsnfsX38	2184delA
c.2657+5G>A (AJ574995.1:g.216G>A)		2789+5G>A
c.2988+1G>T (AJ575003.1:g.305G>T)		3120+1G>T
c.3437delC	p.Ala1146ValfsX2	3569delC
c.3484C>T	p.Arg1162X	R1162X
c.3718–2477C>T (AY848832.1:g.40725C>T)		3849+10kbC>T
c.3846G>A	p.Trp1282X	W1282X
c.3909C>G	p.Asn1303Lys	N1303K

Appendix XII – CF Trust consensus documents, booklets & factsheets

These are available on the CF Trust website – www.cftrust.org.uk/aboutcf/publications/. Can also be accessed via links below if reading this online (CTRL + click on red icon).

Current Consensus Documents

Microbiology

Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis. First edition. September 2010.

Antibiotics

Antibiotic Treatment for Cystic Fibrosis. Third edition. May 2009.

MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA). April 2008.

Bones

Bone Mineralisation in Cystic Fibrosis. February 2007. (Not to be downloaded without addendum, below).

Addendum for Bone Mineralisation in Cystic Fibrosis.

Pseudomonas aeruginosa

Pseudomonas aeruginosa infection in people with Cystic Fibrosis. Suggestions for Prevention and Infection Control. Second Edition. November 2004.

Burkholderia cepacia

The Burkholderia cepacia Complex - Suggestions for Prevention and Infection Control. Second edition. September 2004.

Diabetes

Management of Cystic Fibrosis-related Diabetes Mellitus. June 2004.

Nutrition

Nutritional Management of Cystic Fibrosis. April 2002.

Physiotherapy

Clinical Guidelines for the Physiotherapy Management of Cystic Fibrosis. January 2002.

Standards of Care

Standards of Care - Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK 2001. May 2001.

Nursing

National Consensus Standards for the Nursing Management of Cystic Fibrosis. May 2001.

Booklets

The Facts - An introduction to Cystic Fibrosis
Cystic Fibrosis & You - A guide for children
Growing up with Cystic Fibrosis - A guide for teenagers
My Mummy has CF
Genetics
Health Care Workers with Cystic Fibrosis
Dying, death and bereavement (not available online - please contact the CF Trust to order)

External publications (not published by the CF Trust)

Cystic Fibrosis and Relationships

Fact sheets

A Patient's Charter: The care of patients with Cystic Fibrosis
Benefits
Cascade screening
Cystic Fibrosis Trust Support Services
Cystic Fibrosis and bone health
Cystic Fibrosis-related diabetes
Employment
Exercise
Financial help
Finding out about Cystic Fibrosis
Higher education
Home intravenous therapy (Home IVs)
Housing
Melioidosis and travel to tropical countries
Nebuliser therapy
Nutrition: A guide for adults
Nutrition: A guide for children and parents
Nutrition: A guide for feeding infants
Physiotherapy treatment - Airway clearance
Physiotherapy treatment - For babies and toddlers
Prescription charges (updated April 2010)
School and Cystic Fibrosis

- Steroid treatment in Cystic Fibrosis
- The sweat test in Cystic Fibrosis
- Totally Implantable Intravenous Access Devices (TIVADs) / Ports in Cystic Fibrosis
- Transition from paediatric to adult care: Guide for young people
- Transition from paediatric to adult care: Guide for parents
- Transition from paediatric to adult care: Guide for commissioners and hospital / clinical teams
- Transplantation
- Urinary incontinence in Cystic Fibrosis

Appendix XIII – Useful telephone numbers ☎

Royal Brompton Hospital - 0207 352 8121

	Extensions
Bed Manager	8556, bleep 1234
Biochemistry	8410
Bone densitometry	8965
CF Secretary	8674
Dietitian	8465
Foulis ward (adults)	4821
Haematology	8408
High Dependency Unit	2035
LCI	8233
Lung function	8910
Microbiology	8451
Nuclear medicine	
-- Bone densitometry	8965
-- Ventilation Scans	8666
Pharmacist (paediatric)	4375, bleep 7403 or 7410
Pharmacy (drug information)	8901
Pharmacy (dispensary)	8038, 7777
Physiotherapy	8088
Rose Ward	2410 2411 2412 2413
Ventilation Scans	8666
X-ray (in-patient)	2326
X-ray (outpatient)	4668, 4670 (PACS)

External numbers

CF Trust	0208-464 7211 11, London road, Bromley, Kent BR1 1BY www.cftrust.org.uk
CF Foundation (USA)	www.cff.org
Great Ormond Street Hospital	0207-405 9200
Kennedy-Galton Centre (genetics)	0208-422 8577

Consultant referrals

Adult CF Unit	Dr Di Bilton	0207 352 8121 ext. 4805
	Prof Margaret Hodson	0207 351 8041
	Dr Khin Gyi	0207 352 8121 ext. 4005
	Dr Nick Simmonds	0207 351 8997
Dermatology	Dr Sue Mayou	0207 746 8695
Ear Nose and Throat	Mr Jonny Harcourt	0208 746 8345
	Mr Will Grant	0208 746 8345
Gastroenterology	Dr John Fell	0208 746 8628
	Dr Jenny Epstein	0208 746 8628
	Mr Grant Mallon	0208 746 8627 (or bleep 4988)

Genetics	Dr Sue Holder	0208 869 2796
	Dr Martin Schwarz	0161 701 4921
Growth / puberty / diabetes	Dr Nicola Bridges	0208 746 8885
Gynaecology	Mr Guy Thorpe-Beeston	0208 846 7902
Heart-lung Transplant	Dr Helen Spencer	0207 405 9200
Hepatology	Dr Marianne Samyn	0203 299 1162
	Prof David Westaby	0208 383 4824
Paediatric Surgery	Mr Muntha Haddad	0208 746 8885
	Mr Simon Clarke	0208 746 8696
Radiology	Prof David Hansell	0207 351 8034
Rheumatology	Dr Clarissa Pilkington	0207 829 7887
Thoracic Surgery	Mr Simon Jordan	0207 351 8559
	Mr Mike Dusmet	0207 351 8228
	Mr Eric Lim	0207 351 8591

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Page numbers in bold refer to drug information in Formulary.

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