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

2014

6th edition

The 6th edition of these guidelines has been written by members of the Royal Brompton Hospital Paediatric Cystic Fibrosis Team. Contributors over the years include:

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2nd to 6th 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 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 Foundation Trust in December 2013.

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

Next revision will be published in 2017 so this edition should not be used after that date. Please destroy all 2011 editions.

What's new in the 6th 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, & appendix XIII):

New sections
3.8 Payment by Results – the mandatory tariff (includes the banding definitions).
4.5 Self Administration of Medicines
5.5 What happens when newborn screening results are not clear cut?
6.2a Antibiotic policies & specific organisms
6.2b Drug allergy & desensitisation
6.8 Ivacaftor
6.15b Inhaled antibiotic bronchoconstrictor challenge (Drug Response Assessment)
6.15d Inhaled dry powder antibiotics (& section 6.2a)
6.15e Induced sputum
11.3 Home delivery of medicines

Additional information
When patients with *B.cepacia,* MRSA or *M abscessus* are considered free of the organism (3.1, 6.2a 6viii, 4.7).
Treatment of 1st isolation of *Pseudomonas aeruginosa* in 1st 3 months of life (6.2a).
Treatment of unknown organisms (6.2a).
Achromobacter xylosoxidans (6.2a).
Serratia marcescens (6.2a).
Burkholderia cepacia complex (6.2a)
Scedosporium apiospermum (6.9).
Importance of exercise (6.15a).
Expanded options for airway clearance techniques (6.15a).
Safe use of insulin (8.1).
Terminal care (10.5).
Gene mutation nomenclature (appendix XI).
CF Trust literature – new web links (appendix XII)

New appendices
I. Transition integrated care pathway
III. Home visit report for Challenging CF Protocol
IV. Ivacaftor: proform for commencing / monitoring treatment
VI. National Service Specification
VII. Payment by Results Guidance 2013-14
VIII. Guide for parents starting a child on a nebulised therapy

New drugs
Ivacaftor
Posaconazole

Policy changes / additions: (section number in brackets)

Chapter 3 - How the service runs

- Patients with *B cepacia* are coming to special segregated clinic following MRSA clinic rather than general respiratory clinic (3.1).
- Patients with *M abscessus* will come at the very end of clinic with no-one using the room after them for at least 1 hour (3.1).
- We aim to have patients seen by a consultant alternate clinic visits as a minimum, and a consultant will often speak to the parents in clinic if they have been seen by a trainee (3.1).
- Clinical psychologists are available for annual reviews and also new urgent issues (3.1).
- Weighing children in clinic – those aged >5 years will be weighed in light clothing, whilst those aged 5 or less will be weighed in their underwear (3.1 & 7.1).
- Only send sputum (or BAL) for NTM, not cough swabs (3.1).
- Annual review taking place outside of clinic on Tuesdays or Thursdays (undergoing pilot) (3.2).
- LCI measurements for children aged 5 and above at annual review (3.2).
- Iron studies at annual review – Hb, MCV and ferritin measured (3.2).
- Less blood needs to be taken at annual review (3.2).
- We are carrying out CGMS at home in all 12 & 15 year olds around time of annual review (3.2 & 8.1).
- The Transition Integrated Care Pathway (TICP) (3.3, appendix I).
- CF nurse specialists are extending their attendance at shared care clinics (3.4).

Chapter 4 - Admission to hospital

- New policy of self administration of medicines for in-patients (4.5).
- Patients with *M abscessus* will be kept in isolation on the ward (4.7).
- To suggest that GPs 'surface treat' families of children with MRSA.

Chapter 5 - Making the diagnosis

- Sweat chloride normal level <30 mmol/L applied to all age groups (5.3).
- All patients to have full extended genotyping for potential mutation-specific therapy (5.4).
- Indeterminate newborn screening results. Policy in place for borderline sweat test (30-60 mmol/L) in the presence of zero or one gene mutation; and normal sweat test in the presence of 2 mutations, at least one of which is of uncertain significance (5.5).

Chapter 6 - Respiratory care

- London newborn screening antibiotic protocol adopted into our antibiotic policies for all ages (6.2a).
- Oral antibiotics given for a viral URTI or minor chest exacerbation (with no organism isolated) must be given for a minimum of 2 weeks, but carried on for at least 1 week once the child is symptom-free. If the child still has symptoms at 2 weeks, the CF unit must be contacted. Note we still use 4 weeks of oral antibiotics for exacerbations when specific organisms are isolated (6.2a).
- Flucloxacillin prophylaxis is to be reviewed at 3 years of age and aim to stop it (6.2a).
- We are reducing our use of co-amoxiclav for prophylaxis (6.2a).
- Flucloxacillin treatment is given three times a day but at the same total daily dose as we use now (prophylaxis remains at twice daily (6.2a).
- Nebulised aztreonam now approved for use at Brompton (6.2a)
- Use of dry powder inhaled antibiotics – TOBI podhaler & Colobreathe (6.2a, 6.15d)

- Protocol for antibiotic desensitisation on the ward (6.2b)
- To consider starting DNase daily for all patients when they are 6 years old, whatever their lung function. Additionally it should be encouraged for all our children who are currently older (6.4).
- The default will be to use DNase daily, but consideration of alternate day therapy after 6 months in those who are well or who find the daily treatment a particular burden (6.4).
- Prescribing mechanisms for DNase under PbR (6.4).
- Long term azithromycin used 3 times per week (not daily) (6.7).
- When long term azithromycin is started, consider stopping prophylactic flucloxacillin or co-amoxiclav, unless there is a good reason to continue, ie patient is known to have macrolide-resistant organisms.
- Use of ivacaftor for patients aged 6 and above with G551D gene mutation (6.8).
- We no longer routinely measure itraconazole blood levels (6.9).
- Posaconazole to be considered as 3rd line agent for ABPA (6.9).
- Atenolol for haemoptysis can be considered (6.10).
- Concerns over increased risk of NTM with oral and inhaled steroid use (6.12).
- Consideration of inhaled tiotropium for intractable wheezing (6.12).
- Use of induced sputum for microbiology prior to proceeding with a bronchoscopy (6.14, 6.15e).
- Inhaled antibiotic bronchoconstrictor challenge (Drug Response Assessment) – new pass/fail definition (6.15b).
- Staged approach to starting nebuliser therapy in a young child (6.15c, appendix VIII).

Chapter 7 - Gastrointestinal & nutritional care

- Aquadeks will be offered to all newly diagnosed babies as an all in one vitamin supplementation (7.1).
- Pancreatic sufficient babies will now receive vitamin D from diagnosis in the form of Aquadeks to promote bone health (7.1, 8.4). Older PS children will receive Vitamin A+D capsules (unless vitamin A levels are high) (7.1, 8.4).
- Vitamin K will be routinely given to all patients (including pancreatic sufficient) when 6 years old (7.1, 8.4).
- Weighing children in clinic – those aged >5 years will be weighed in light clothing, whilst those aged 5 or less will be weighed in their underwear (7.1).
- No longer measuring 3 day faecal fat, although single-sample stool fat microscopy may need to be repeated on more than one day (7.1).
- Algorithm for weight loss or lack of weight gain (7.1).
- In newborn screened babies initially found to be pancreatic sufficient, stool elastase will be repeated routinely at 3 months and 1 year (7.2).
- We are now only measuring Hb, MCV and ferritin to assess iron status at annual review (7.8).

Chapter 8 - Other non-pulmonary complications of CF

- Updated WHO definitions of diabetes (8.1).
- Oral glucose tolerance test – we now measure Glu at 60 as well as at 0 and 120 mins. If cannula in place we will measure at 30 min intervals. Fasting OGTT preferred to non-fasting (8.1).
- See above (3.1) for CGMS screening policy in 12 & 15 year olds (8.1).
- See above (7.1) for changes in routine vitamin D and K supplementation policy (8.4).
- Clarification that Vitamin D levels <50 will always be treated with colecalciferol, whilst levels 50-75 will have an increase in routine supplementation (8.4).

Chapter 10 - Miscellaneous

- Not recommending intranasal influenza immunisation until evidence available for its use in CF. We recommend continuing with the injectable form. (10.2)

Chapter 11 - Drug formulary

- Ciprofloxacin dose is 20 mg/kg BD (750 mg BD max) from 1 month and older (11.1b).
- Oral clarithromycin dosing by weight not age (11.1b).
- Colomycin® (Colistin) nebulised dose is 1,000,000 units for all children <8 years old, and Promixin® dose is 500,000 units for all <8 years (11.1c).
- *M abscessus* therapy – intensive phase intravenous therapy is now 2 weeks (not 3) to increase tolerability of the drugs (appendix II).

Formulary

Additions	*Changes*
• Aminophylline (IV) • Aquadeks • Colobreathe • Ivacaftor • Mannitol (inhaled) • Posaconazole • TOBI podhaler	• Aztreonam IV dose CIVAS bands • Azithromycin now 3x per week not daily • Ciprofloxacin dose • Clarithromycin dose • Co-amoxiclav dosing includes 125/31 & 250/62 oral suspension • Colistin nebuliser dose 1mU for all those under 8 years • Flucloxacillin treatment now TDS • Vitamin D clarified • Voriconazole dose

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 Specialist Commissioners, NHS England.

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, trainee doctors, nurse specialists, dietitians, physiotherapists, clinical psychologists, pharmacists and social workers. 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). We are happy to continue with a shared care policy, as long as the national Service Specification and our signed Service Level Agreement are adhered to. We also run a number of out-reach clinics whereby our MDT 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 9000 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 finish their GCSEs and usually by 17 years of age. Follow-up is then offered in the adult clinic at the Royal Brompton Hospital or another Specialist Adult Centre of their choice.

2. Department staff and contact numbers

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Paediatric CF Nurse Specialists – Bleep1213, Exts 8755, 2812 (internal only)

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Bleep 7032, Ext 4053

Specialist Registrars -	Bleep on-call SpR for Respiratory paediatrics - 1237 via hospital switchboard
Physiotherapists -	**Nicola Collins** n.collins@rbht.nhs.uk Bleep 7304, Extension 8088
Home care physiotherapists -	**Emma Dixon** e.dixon@rbht.nhs.uk 07970 269 452 **Nicky Murray** n.murray@rbht.nhs.uk 07791584749
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Family Liaison Service (Rose Ward)	**Jane Docker** j.docker@rbht.nhs.uk Extension 8588, Bleep 1274 **Nicola Jones** n.jones3@rbht.nhs.uk Extension 8588, Bleep 1250
Welfare Rights Officer	**TBA** Ext 4736
Social workers	**Gail Frampton** Gail.frampton@rbkc.gov.uk 0203 315 5978 or 07837255781 **Gabriela Grigore** Gariela.grigore@rbkc.gov.uk 0203 315 1179 or 07817104569
Named nurse for child protection	**Tracy Foster** t.foster@rbht.nhs.uk Ext 2903
Wards	Rose Ward 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 CF 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
	Mr Elliot Benjamin	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
Palliative care	Dr Anna-Karenia Anderson	Royal Marsden Hospital
Paediatric Surgery	Mr Simon Clarke	Chelsea & Westminster Hospital
	Mr Muntha Haddad	Chelsea & Westminster Hospital
Radiology	Prof David Hansell	Royal Brompton Hospital
	Dr Simon Padley	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 4.7). 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.

Children with *Burkholderia* species and MRSA do not attend the routine CF clinics. These patients will attend clinic on the 2nd Friday of each even month (Feb, April, June, Aug, Oct, Dec). Patients with MRSA will be booked into earlier time slots and those with *B Cepacia* having later time slots. Due to the adult *B Cepacia* clinic being held downstairs, patients will be advised to come in via Fulham Road entrance and go straight up the stairs and through physiotherapy into clinic. The HCA/Nurse will take prescriptions down to pharmacy so they do not mix with patients waiting downstairs.

Patients with *M abscessus* will come to the END of a clinic and will be the last ones in their room. No-one to use the room after them for at least 1 hour.

When can patients rejoin the usual CF clinic?

- *B cepacia:* when they have been free of the organism for 1 year, with at least 3 negative sputum or cough swabs or BAL samples in that year. Caution though if the original isolation was on sputum or BAL, and subsequent samples are cough swabs only.
- MRSA: when they have had 3 negative swabs (see hospital policy http://www2.rbht.nhs.uk/services/infection-control/mrsa/, dated Jan 2012).
    - If MRSA on skin swabs only – follow Brompton hospital policy.
    - If MRSA on sputum/cough swab/BAL – 3 negative respiratory samples, each one taken at least 1 week apart. Caution again as for *B.cepacia* re type of respiratory sample obtained.
- *M abscessus:* considered free when they have had 4 negative samples over 1 year since their 1st negative sample See also sections 4.7 and 6.2a part 6.VII.

There is a joint CF diabetes clinic on the 3rd Friday of the month at RBH.

Patients may attend either clinic at their convenience although we encourage continuity where possible. Most children are seen in a CF clinic every 2 months, or every 3 months for those recognised to have very 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 alternate visits. We aim for all patients to be seen at by the full RBH MDT 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 the patient's named consultant.

The families see the following:

Doctor. This may be a consultant (Mondays –Bush, Davies, Carr, Chavasse, Greenaway; and Fridays –Rosenthal, Balfour-Lynn, Carr & Charlton, 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. We aim to have patients seen by a consultant alternate visits as a minimum, and a consultant will often speak to the parents in clinic if they have been seen by a trainee.

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 clinic letters and write the annual review reports.

Health Care Assistant. To measure height and weight, oxygen saturation by pulse oximetry.

Respiratory physiologists. To measure lung function.

CF nurse specialist. To see all patients and provide general information and support. Portacaths may be flushed if required.

Physiotherapist. All the children should be seen by a physiotherapist to review techniques, and to obtain sputum or cough swab specimens.

Dietitian. All pancreatic insufficient patients and all babies are seen by the dietitian, for review. It may not be necessary to be seen every clinic visit.

Clinical psychologists. They are available for annual reviews and also new urgent issues. They may be able to meet any patient or their family but it is helpful if they are contacted in advance so they can book a time for an appointment in the clinic.
.
Play specialist. Is available to help with distressing procedures such as blood taking

Others. The social worker or Welfare Rights Officer Carol Wingett can also meet parents and often help guide them 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 aged 5 years or less are always weighed in underwear, those older than 5 in light clothing. All children have their height measured on a stadiometer. Head circumference should be measured in children less than 1 year of age.
- Children over 4-5 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. Only sputum is sent for culturing NTM (cough swabs are always negative for this).

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

Shared care clinics

We conduct joint clinics with many of our shared care hospitals. We aim to take the full Brompton MDT with us to the clinics to work alongside the local consultant and their MDT.

The clinic should follow the same format as our own clinics, including the emphasis on patient segregation.

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. Currently this takes place in the normal CF Clinic, but we are piloting a new scheme which we hope to start in 2014. The annual review will take place as a day case, in the Sleep Unit, with all the consultations and investigations happening between 10am and 3pm. The family will then come back to clinic 4-6 weeks later (or be seen in a shared care clinic) by their named consultant, who will have all the results available, and will agree a plan and write the report.

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 children will be seen for the following:

- Discussion with the nurse specialist following the PortCF proforma. This will include the number of IV and oral antibiotic courses, usual symptoms and microbiology. The CF Trust Database forms are also filled in which is mandatory in order to put full data onto PortCF.
- 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.
- All patients are now offered the opportunity to meet with a Clinical Psychologist as part of their annual assessment**.** This informal discussion will hopefully find out whether there are any issues the families wish to discuss in more detail and then to arrange a suitable follow-up appointment. If the families are already meeting with a psychologist, 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 only needs to breathe normally through a mask or mouthpiece.

  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 and we intend to carry out in all children aged 5 years 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).

  In an older child with known poor lung function, there is less point in carrying out LCI as well.

- *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 not scored but we record changes and differences from the last year.

- *Ultrasound liver and spleen*. Liver ultrasound is 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 anyone else 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 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 (see section 8.4). 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 (section 8.1) they should be considered at annual review. We may decide to carry out CGMS (continuous glucose monitoring system) in some patients, and are now going to carry out a CGMS at home in all 12 and 15 year old patients as a screening procedure (assuming they have not had one done recently). See section 8.1.

- *Sputum or cough swab* for microbiology, and sputum only for NTM.

- *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 ferritin
    - IgG, IgA, IgM
    - IgE
    - Aspergillus RAST (specific IgE)
    - Aspergillus IgG (ICAP)

Blood bottles: 2 (red) EDTA bottles, 4 (brown) SERUM bottles (6 in older children), 1 (green) COAGULATION bottle. Bottles must be full. Use larger bottles in older children.

PortCF

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All data is entered on to our own hospital database and the UK CF national registry (PortCF), for which the parents will have given written informed consent. This is mandatory and determines patient banding and payment to the hospital via the PbR system (see section 3.8). Website – www.portcf.org.uk. User name for staff to access our data can be obtained from our Database Manager.

3.3 Transition from paediatric to adult care

Transition from paediatric to adult care is discussed with all patients and their families from an early age; however a more detailed discussion takes place from about 14 years onwards. The transition process has been divided into two parts: pre-transition and transition. Invitations to attend a pre-transition clinic are sent to all 15 year olds, this is an opportunity to meet the adult CF team and ask any questions before attending the transition clinic. Invitations are sent for the transition clinic at around 16 years of age; details included with this invitation outline the choices 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 (www.rbht.nhs.uk/cf-transition/). 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. The Transition Integrated Care Pathway (TICP) is part of this document and is commenced at this time (Appendix I).

Transition clinics are held on Monday and Friday afternoons in the usual paediatric clinic area. There are about 4-5 clinics per year. The adult CF Team (consultant, nurse specialist, physiotherapist and dietitian) attend each transition clinic to give patients and families an opportunity to meet and ask questions about the move to adult care. The adult consultants who attend transition clinics are either Dr Diana Bilton or Dr Nick Simmonds. The patients remain under the care of the paediatric team until they are seen for the first time in the adult clinic.

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

If or when patients need admission to Foulis ward, our hospital school teachers visit regularly (and liaise with schools and colleges) to continue education for A levels (exams are taken on the ward if necessary), and university / college. The school also provide a careers advisor. A leaflet outlining educational support is available on the ward on the adult CF team website (www.rbht.nhs.uk/patients/condition/cystic-fibrosis/cystic-fibrosis-transition/the-role-of-the-hospital-school/).

Segregation policies during admission can be a problem for these young people, as they value support from each other. To help with this, a Foulis ward blog has been developed to improve communication between in-patients. At admission every patient (regardless of age) is asked to sign a 'contract of care', which sets out activities expected from patients during admission (including adhering to cross infection policies). In addition there is a list of what patients can expect from the CF team.

3.4 Homecare & Outreach 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 two trained children's nurses both with a children's community nursing qualification; two physiotherapists (who job share) specialising in providing homecare for children with CF and their families; and a new addition of a community dietitian. Criteria for referral are that the child attends RBH as their specialist centre assuming distance is not prohibitive.

The Nursing service core hours are Monday to Friday 9am to 5 pm.
The Physiotherapy service operates Tuesday to Friday 9am to 5pm.

Contact for families and professionals is via mobile telephone (with answerphone); messages left within the hours of 9am to 5pm will be answered the same day (weekdays).

07973 173 969	**Pat Stringer** (Nurse Specialist)
07971 224 068	**Karen Henney** (Nurse Specialist)
07794 676 858	**Katie Dick / Laura Hayers** (Nurse specialists)
07970 269 452	**Emma Dixon** (CF Physiotherapist)
07791 584 749	**Nicky Murray** (CF physiotherapist)
	Heidi Cram (CF dietitian)

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
  - preparation for transition
- 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 health 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.
- Training of local teams

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 before or 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 nursing team are available to visit GP surgeries a visit if required 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.
- The team are currently extending their attendance at shared care clinics and continue to act as a resource for shared care teams

Liaison with the multi-disciplinary team at the RBH –

- The team works closely with the hospital-based CF clinical nurse specialists.
- The team has direct access to medical advice at RBH at all times, and will consult with medical staff from the home as appropriate.
- Nursing 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/or other carers. They provide a service to both inpatients and outpatients. They are available during CF clinics if required (it is always advisable to ring prior to the clinic appointment to ensure someone is available). They also offer a consultation service to other

members of the CF team and are available 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 their family in a variety of ways. They offer the opportunity to discuss anything which can arise when a child and family are living with CF (or anything else - it need not be related to CF). As well as talking and listening, clinical psychologists can offer suggestions for change and practical ways for coping with difficult situations such as managing invasive procedures (especially blood tests). Any assessments and interventions carried out would be made sensitive to the needs of the child and/or family. Confidentiality is respected and discussed with each person seen, but it can often be helpful to share some information with other members of the CF team (e.g. what works well to help a child co-operate with their blood test). Permission from parents would be sought prior to a clinical psychologist formally introducing her/himself to a child. Sometimes the psychologists will liaise with local counselling/mental health services because long term follow up is often better carried out nearer to the family's home. This would not be done without the permission of the patient and/or their family.

Some reasons for referral or consultation include:

- Coping with the new diagnosis of CF; the psychologist meets the family of newborn screened babies during the education days and will meet families of older children also.
- Informing friends and family about the 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.
- Consideration of future treatments that may be offered along with the implications e.g. DNase.
- Managing invasive procedures- including fear of needles.
- Feeding/nutrition.
- Helping children swallow their prescribed medications as tablet/capsule form ('Pill School').
- Life changes, for example transferring to secondary school.
- School problems.
- Mood problems.
- Changes in behaviour/personality which may or may not be associated with the CF.
- Considering transplantation.

3.6 Social work support

The Paediatric Social Worker (based at Chelsea and Westminster Hospital, Social Work Department, Health Link Team) is a member of the multidisciplinary team. The Health Link Team operates both in the hospital setting and in the community in central and south of Royal Borough of Kensington and Chelsea (RBKC). The Paediatric Social Worker will work and accept referrals for those children and their families that live in RBKC area or are long term inpatients at the Royal Brompton Hospital and there are concerns:

a) that a child is seen as being a child in need as a result of his disability, or because his health and development is likely to be significantly impaired, or further impaired, without the provision of services (Section 17, Children Act 1989).

b) that a child is suffering or is likely to suffer significant harm. (Section 47, Children Act 1989).

The remit of the Children Social Work Department is defined by legislation and the main legislative act that the Paediatric Social Worker works under is Children's Act 1989 and 2004.

The Social Worker's role is primarily to undertake an assessment of needs and to provide services (if resident in RBKC area), if required, whilst the child is an inpatient in the hospital and/or at the point of discharge from the hospital.

Social Worker's role includes:

- Supporting very sick children, children with special needs, and their families that are long term inpatients and linking them into their local services (they can be either RBKC or non RBKC residents).

- The Paediatric Social Worker will meet with the child and family and liaise with the necessary hospital and community professionals to determine if an assessment of needs is required. If an assessment of needs is required this will involve gathering information from the child, family and also all relevant hospital and community professionals. An assessment of needs will usually be undertaken if a child is a long term inpatient at the Royal Brompton Hospital or if the child is resident in RBKC area.

- If the child is a long term inpatient and not a resident within RBKC area, the Paediatric Social Worker, after undertaking an assessment and/or at the point of discharge, will refer the child and his family to his home Local Authority's Children Social Work Department with the recommendation that further assessment of needs or provision of services is required.

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

- Accepting child protection referrals for children that live in RBKC area and undertaking child protection investigation (Section 47, Children Act 1989) concerning these children. In child protection cases concerning children who are not resident in RBKC area we act as liaison with the home Local Authority until responsibility is agreed.

- Helping health staff collate evidence regarding concerns about children and their parents/carers

- Supporting health staff referring child protection concerns to home Local Authority' Children Social Work Departments.

- Supporting health staff with homeless families, and thus with no Local Authority, and linking the families into community services.

- Attending regular meetings with Royal Brompton Hospital wards and providing advice and support to staff.

- Attending Professionals, Discharge or Multi-Disciplinary meetings where there is a concern about a child/family, supporting health staff during the meeting.

3.7 Family Liaison Team & Welfare Rights Adviser

The family liaison team 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 also may cause extra financial burdens. Their aim is to try to alleviate that stress. If they cannot help, they usually know someone who can!

The Welfare Rights Adviser provides welfare advice to paediatric patients and their families on the following issues
- financial concerns.
- benefit advice and assistance with applications.
- housing issues.

3.8 Payment by Results – the mandatory tariff.

Since April 2013 there has been a mandatory tariff paid via the Specialist Commissioners to the CF centres, based on a year of care tariff that is dependent on the severity of the child's CF disease. This is determined by the complexity adjusted yearly banding system (see below) produced from data entered on to the CF national registry (PortCF). It is critical data is entered for every patient without exception, assuming consent obtained, usually by January 31st each year with the previous year's data.

This is to cover CF related care only (e.g. not A&E visits or admissions for trauma or non-CF illness). It also specifically excludes charges for high cost drugs – DNase, nebulised antibiotics (colistin, tobramycin, aztreonam), mannitol and ivacaftor.

Part of the tariff is paid to our shared care Network Centres. Each centre must comply with the national Service Specification (appendix VI), the CF Trust Standards of Care (2011), and the Service Level Agreement signed with the Brompton. The paediatric tariff does not take into account the extra costs incurred by shared care arrangements nor costs of local community services.

Banding definitions		Band						
		1	1A	2	2A	3	4	5
Therapies	Maximum number of total days of IV antibiotics	0	14	28	56	84	112	≥113
	Nebulised antibiotics (*Pseudomonas* infection)		Yes					
	Long-term (>3 months) nebulised antibiotics or DNase			Yes				
	Long-term (>3 months) nebulised antibiotics and DNase				Yes			
Hospitalisations	Maximum numbers of days in hospital	0	7	14	14	57	112	≥113
Supplemental feeding	Nasogastric feeds				Yes			
	Gastrostomy					Yes		
Complications	CF Related Diabetes or ABPA w/o other complications				Yes			
	CF Related Diabetes and ABPA					Yes & (FEV_1 ≥60%)	Yes & (FEV_1 <60%)	
	Massive Haemoptysis or Pneumothorax					Yes & (FEV_1 ≥60%)	Yes & (FEV_1 <60%)	
	CF Related Diabetes and Gastrostomy					Yes & (FEV_1 ≥60%)	Yes & (FEV_1 <60%)	
	Non Tuberculous mycobacterium treated or difficult to treat infections (e.g. MRSA or Cepacia) requiring other nebulised antibiotics e.g. Meropenem, Cayston, Vancomycin.					Yes		

Banding definitions

In appendix VII, we have enclosed the section on CF from the Payment by Results Guidance for 2013-14, published in Feb 2013 by the Dept. Health. The full guidance is available on - www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf.

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 1 monthly admission for IV methylprednisolone (usually 3 nights).
- 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.

Clerking -

On admission, the reason for hospital attendance must be identified, and documented clearly in the integrated care pathway (ICP), which is available on the intranet and on Rose ward). Clerking and all subsequent documentation for that admission should be contained within the ICP. Medical admission paperwork covers the following information.

- **Allergies** – 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.
- **Reason for admission** (tick box).
- **Current CF complications** (tick box).
- **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.
- **Current medication -**
  - 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.
  - Write inhaled steroids doses in mcg **not** number of puffs.
  - If a patient is on oral steroids, record the starting date and dose/kg/day.
  - Drug doses are often recorded in the last clinic letter **but** should be checked directly with the patient or their parents before recording and prescribing them.
  - Check whether there have been problems with aminoglycoside levels in the past.
  - **Inhaled antibiotics**
    - **No-one can receive a nebulised drug if it is being given intravenously**.
    - If they are on IV tobramycin they receive nebulised Colistin (even if that is the month they would have been due nebulised Tobramycin

        - If on IV colistin they receive nebulised tobramycin rather than nebulised colistin. If they have not had nebulised tobramycin before, then they have no nebuliser whilst in.
        - The same applies to dry powder inhalers.
    - Drug histories are confirmed by a pharmacist at the earliest opportunity within pharmacy opening hours.
- **Date of last admission.**
- **Last Sputum/cough swab obtained.**
- **Is annual assessment due soon?** – if so, investigations should be arranged during admission.
- **Best FEV_1% and FVC% in last year.** The respiratory physiologists are able to provide a trend graph.
- **Documented concerns about weight and height. Growth chart are now being kept in the notes.**
- **Recent microbiology** – growths and sensitivity/resistance. The most recent positive sputum culture result should be documented with full sensitivities. Certain bacteria like *B cepacia* complex, MRSA and *M. abscessus* require specific action with regards to therapy and isolation from other CF patients.

History

- 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.
- 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 underwear when aged 5 or under, and light clothing aged over 5. 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, INCLUDING weekends** (use the ward spirometer).

Admission bloods. These are generally performed at the same time as the first aminoglycoside level (pre-2nd dose) 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 is used immediately before the procedure, but 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)**	**Biochemistry**
• **Calcium, magnesium, phosphate**	**serum (brown)**	**3 ml minimum**
• **Glucose**	**serum (brown)**	**(alternatively**
• **HbA_{1c}**	**serum (brown)**	**lab will accept**
• **Total IgE**	**serum (brown)**	**clotted blood)**
• **Aspergillus RAST**	**serum (brown)**	
• **CRP**	**serum (brown)**	
• **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 immunoglobulins, 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, liver ultrasound or DEXA scan, 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 detection 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:

- Weekly sputum / cough swab, and at point of discharge.
- Daily SpO_2 unless initial one >95%.
- Twice weekly spirometry (Tues, Fri).
- Twice weekly weight (Tues, Fri), those aged 5 or less in their underwear, those older than 5 in light clothing.
- Daily BP and urinalysis if on oral steroids.
- Overnight SpO_2 (Nelcor) early in admission, especially if FEV_1<50% or resting SpO_2 <92% (see section 6.16).

Drug monitoring

Aminoglycosides (Tobramycin, Amikacin)

- Pre-dose levels 23 hours after 1st dose (i.e. before 2nd IV dose). If in desired range, repeat 1 week later; and 1 week after that if having 3 weeks antibiotics. **Record results on drug chart.** See section 6.2a, part 6.IIIg.

IV Polymyxins (Colistin)

- Once weekly U + Es

Chloramphenicol

- 3-weekly WBC, so not routinely required unless having >2 week course

Linezolid

- Weekly FBC

Voriconazole

- Monthly LFTs + FBC

Itraconazole

- Monthly LFTs

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 seen to have achieved competency under the supervision of an SpR.

Whatever grade of doctor, **no more than three attempts of line insertion** should be tried before asking for additional support from colleagues. The line insertion is the most anxious part of the admission, and if it goes badly can often set the tone for a difficult admission, and future problems.

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 20mg) 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). As much as possible, discuss the location of the long line with the patient so as not to impact on their daily routines during treatment i.e. avoid ankle lines in athletic children.

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, filter needle x1, fenestrated drape x 1
- surgical gown
- sterile gloves
- disposable tourniquet
- chlorhexidine swab stick x 2
- non-toothed forceps
- sterile scissors
- 1 x pack
- steristrips
- clear sterile dressing (IV 10000 or Tegaderm depending on the child's allergy status)
- 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) pull back a few millimetres then readvance b) stroking the arm along the line of the vein, c) moving the arm from the shoulder, d) 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. Pull back the introducer sheath and split to remove from line. Apply gentle pressure to the exit site to stop bleeding. Secure the line in place initially with steristrips over the insertion site. Cut a small piece of gauze on which to place the bevel of the long line prior to securing with a sterile clear dressing. Flush the bionector and connect to the line before covering the whole dressing with a bandage.

If insertion of a longline is unsuccessful, consider a short cannula while alternate means of access are considered so as not to delay the start of treatment. Anaesthetic teams can be very helpful particularly if central access is required. If IV access is becoming an issue for a patient, the discussion around portacath insertion should start.

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 (see section 6.2d).

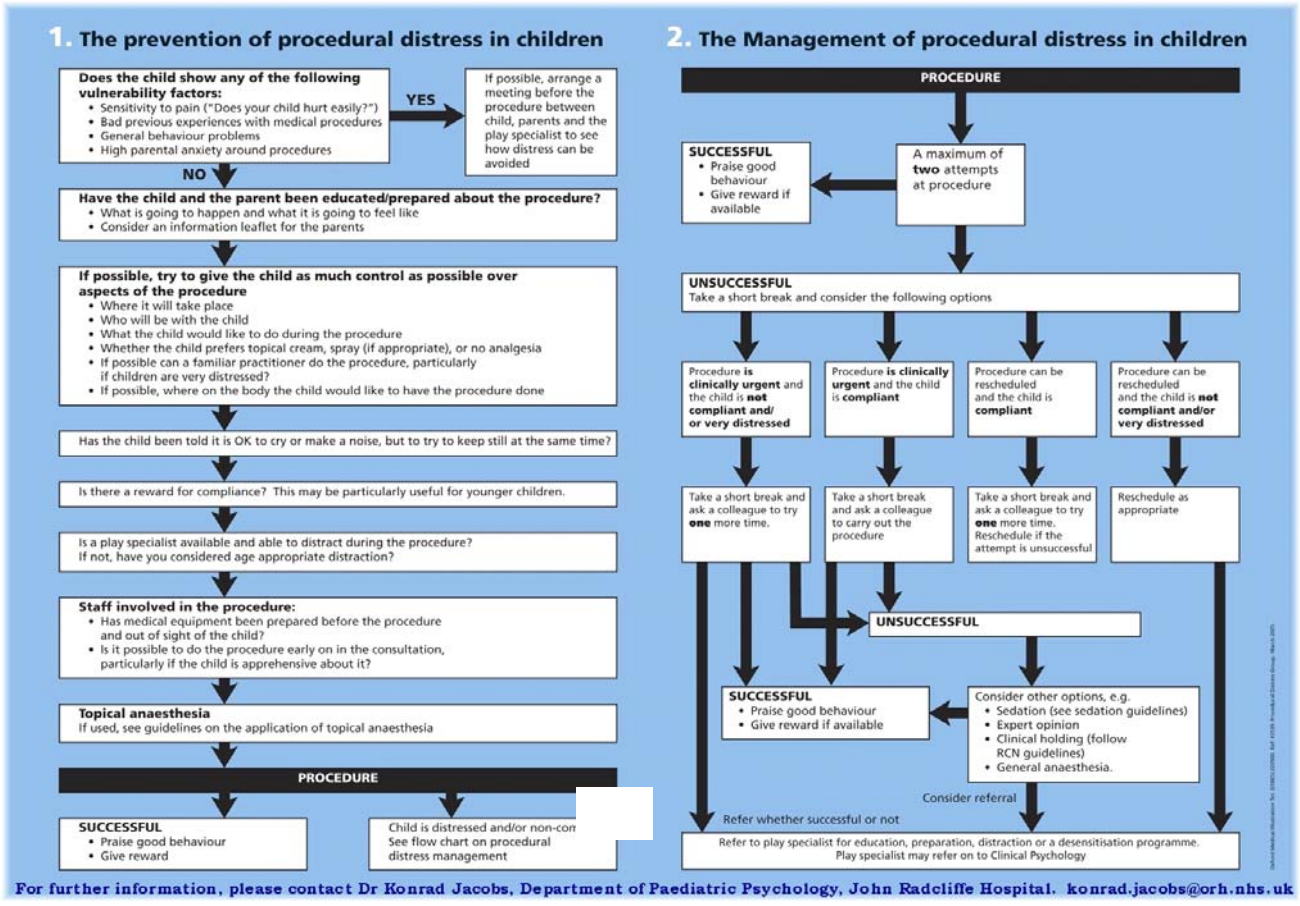
4.4 Procedural distress

Preparation and planning with the child and family is essential to help them to cope. Try to ensure that the play specialists and/or clinical psychologists are involved. 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.
- 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.
- 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 Self Administration of Medicines

The Self Administration of Medicines (SAM) scheme is a means of preparing patients and their parents/carers for continuing care and discharge by ensuring that they have sufficient knowledge about their medicines and the practical skills to comply with their therapy. The SAM scheme encourages patients/parents/carers to take more responsibility for their own medicines whilst they are still inpatients. Another useful aspect of the SAM scheme is that it may alert healthcare staff to any problems the patient/parent/carer may have in adhering to the medicine regimen. It also helps to identify patients who require additional support or other strategies to ensure adequate pharmaceutical care in the home.

For the purposes of the pilot scheme, self-administration will only be commenced during Monday to Friday between 9am and 5pm. However, if a patient has been enrolled in the SAM scheme, this should be continued after these times and on the weekends.

Full details are available on the intranet in the 'Medicines Management Policy for the Self-Administration of Medicines in Children'. Below is a selection of details.

Criteria for patient selection

- All patients/parents/carers that will be responsible for administering their own medicines at home should be considered for inclusion in the SAM scheme.
- The decision to enrol a patient onto the SAM scheme must be discussed with the multi-disciplinary team.
- Signed consent must be obtained.

The following groups of patients will not be included in the scheme:

- Patients under 12 years of age or not deemed responsible following assessment cannot administer their own medicines, however may be included in the scheme if their parents/carers are assessed as competent.
- Patients/parents/carers who are confused must not be given custody of their medicine.
- Patients/parents/carers expressing suicidal/self-harm tendencies should not take part in the scheme.
- Patients/parents/carers with unstable medication requirements.
- Patients/parents/carers who will not be responsible for administering their own medicines at their homes after discharge from hospital.
- Patients/parents/carers that are unable/ unwilling to agree to participate in a self-administration scheme.
- Patients/parents/carers with a past history of drug or alcohol abuse do not have to be excluded from the SAM scheme but the need for extra supervision and reinforcement of education should be highlighted and documented.

Assessment

The assessment of the patient/parent/carer to be enrolled on the SAM scheme should be carried out on admission by the nurse responsible for the care of that patient using the self-administration tool in the Integrated Care Pathway. In certain circumstances, the decision to enrol the patient on the scheme can be made later on in their stay.

The initial assessment/consent from patients/parents/carers may be obtained at an MDT pre-admission meeting.

Throughout the period of self-administration the patient/parent/carer must be assessed by the nurse **at least daily first thing in the morning** as part of the ward routine. The patient's condition and level of supervision required to self-administer medicines may change.

If a parent/carer is administering medicines, and will be away from the hospital for a period of time, then the level of SAM will need to be revised for that period of time

After assessment, patients fall into one of the following categories –

Level	Responsibility for Administration	Responsibility for Storage	Responsibility for Signing Drug chart
0	Nurse	Nurse	2 Nurses
1	Patient/parent/carer And Supervising Nurse	Nurse	1 Nurse & patient/parent/carer
2	Patient/parent/carer And Supervising Nurse	Nurse	1 Nurse & Patient/Parent/Carer
3	Patient/parent/carer	Patient/parent/carer	Patient/Parent/Carer

Other information

- Education / information should be provided by the ward pharmacy team as part of the routine pharmacy service. If these staff are unavailable e.g. outside of normal working hours, then the nurse should provide this information.

- All medicines to be self-administered must be prescribed on the in-patient medication chart.

- As a rule, medicines suitable for the SAM scheme are those that are likely to be used on discharge, medicines that the patient/parent/carer has experience of administering prior to admission or medicines that the patient wishes to use in order to empower them to manage their condition e.g. analgesics.

- Patients/Parents/Carers will be encouraged to bring current medication supplies from home.

- Medicines to be used under the SAM scheme should be stored in the Patient's Own Drug locker. Fridges are currently not available in individual bed spaces and therefore certain drugs should be stored in the designated ward fridges until required for administration.

- Controlled Drugs **may not** be self-administered as part of the SAM scheme.

- Intravenously administered medicines **may not** be self-administered as part of the SAM scheme. However an exception to this is where patients/parents/carers are being trained to administer IV medicines so that they may be administered at home

- The in-patient medication chart for patients/parents/carer enrolled in the SAM scheme at levels 1 and 2 will be signed for by both the nurses and patient/parent/carer.

- Patients/parents/carers self-administering at level 3 will record administration directly on the in-patient medication chart using the endorsement 'Self' and signing beside this endorsement.

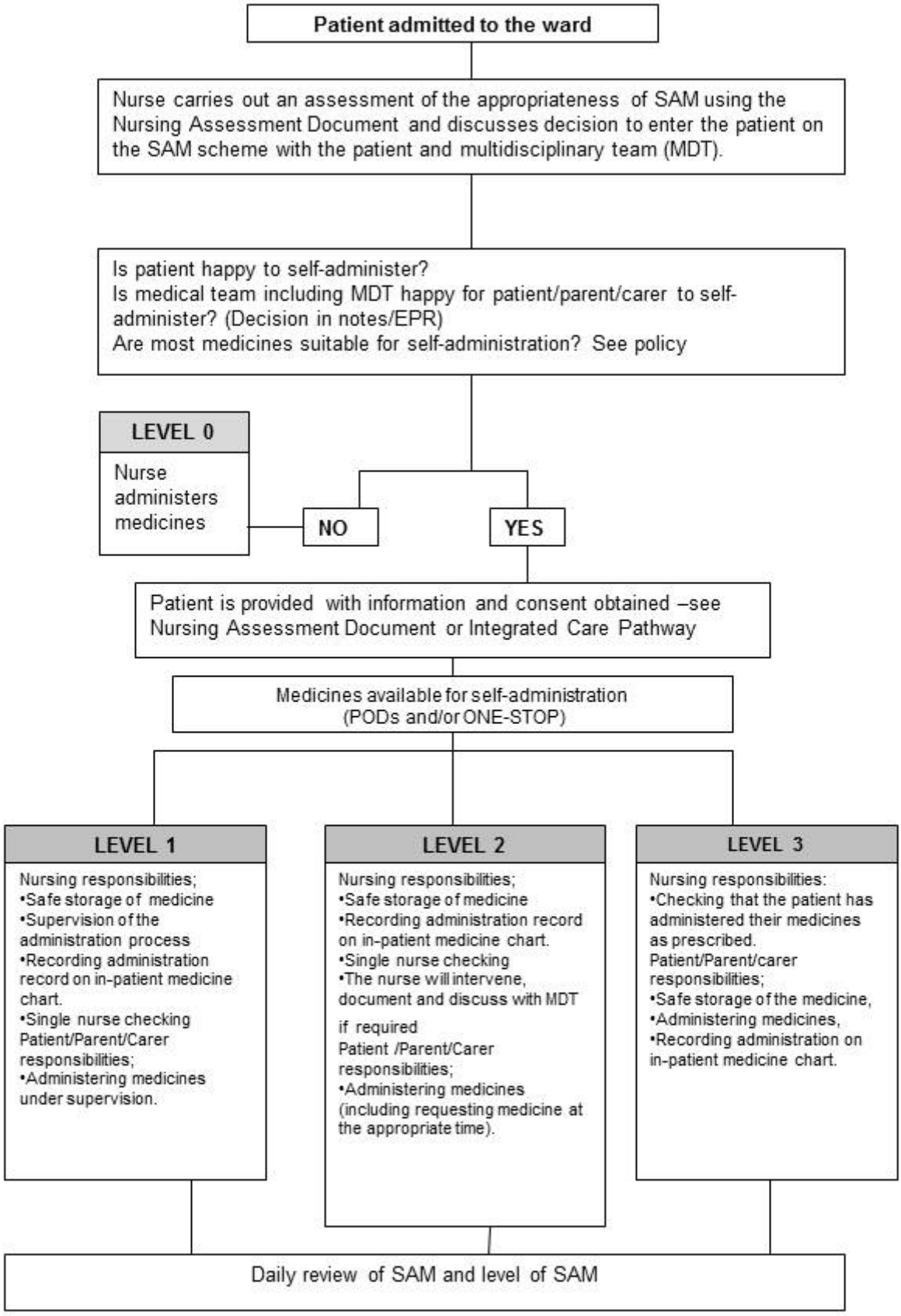
- Administration should be checked for patients self-administering at level 3 at the following set times: **10:00; 15:00; 19:00 and pre bedtime** (this will vary from child to child) so that this will encompass a majority of administration times.

The doctor's role within SAM scheme

- The Consultant with the responsibility for the individual patient's hospital admission must be consulted before the decision is made to enter their patient/parent/carer on to the SAM scheme.

- The Consultant has the right to stop any patient/parent/carer under their care to enter the SAM scheme. Any such decision should be clearly documented and communicated to the admitting team.

- The Doctor should always discuss changes to the patient's medication therapy with the patient and inform the nursing staff of prescription alterations.


Patient admitted to the ward
Nurse carries out an assessment of the appropriateness of SAM using the Nursing Assessment Document and discusses decision to enter the patient on the SAM scheme with the patient and multidisciplinary team (MDT).
Is patient happy to self-administer?
Is medical team including MDT happy for patient/parent/carer to self-administer? (Decision in notes/EPR)
Are most medicines suitable for self-administration? See policy
LEVEL 0
Nurse administers medicines
NO
YES
Patient is provided with information and consent obtained –see Nursing Assessment Document or Integrated Care Pathway
Medicines available for self-administration (PODs and/or ONE-STOP)
LEVEL 1
Nursing responsibilities;
•Safe storage of medicine
•Supervision of the administration process
•Recording administration record on in-patient medicine chart.
•Single nurse checking
Patient/Parent/Carer responsibilities;
•Administering medicines under supervision.
LEVEL 2
Nursing responsibilities;
•Safe storage of medicine
•Recording administration record on in-patient medicine chart.
•Single nurse checking
•The nurse will intervene, document and discuss with MDT if required
Patient /Parent/Carer responsibilities;
•Administering medicines (including requesting medicine at the appropriate time).
LEVEL 3
Nursing responsibilities:
•Checking that the patient has administered their medicines as prescribed.
Patient/Parent/carer responsibilities;
•Safe storage of the medicine,
•Administering medicines,
•Recording administration on in-patient medicine chart.
Daily review of SAM and level of SAM

4.6 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 - This will be linked with the computerised pharmacy discharge system (JAC).
- Ensure you fill in JAC section on 'Any changes to therapy'.
- 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 before discharge. A copy should then be filed in the patient's notes by the ward clerical staff and published onto EPR.

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

4.7 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. Segregation is in place in clinic and for in-patients, including in the school rooms etc to minimise contact between CF patients. There is a 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 also separate children with CF from those with non-CF bronchiectasis/PCD.
- 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. USE THEM!
- 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 *Burkholderia cepacia* and *M abscessus* 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).
- When can patients be considered free of their organisms?
  - *B cepacia:* when they have been free of the organism for 1 year, with at least 3 negative sputum or cough swabs or BAL samples in that year. Caution though if the original isolation was on sputum or BAL, and subsequent samples are cough swabs only.
  - MRSA: when they have had 3 negative swabs. If MRSA on skin swabs only – follow Brompton hospital policy(see hospital policy. http://www2.rbht.nhs.uk/services/infection-control/mrsa/, dated Jan 2012). If MRSA on sputum/cough swab/BAL – 3 negative respiratory samples, each one taken at least 1 week apart. Caution again as for *B.cepacia* re type of respiratory sample obtained.
  - *M abscessus:* considered free when they have had 4 negative samples over 1 year since their 1st negative sample. See also sections 3.1 and 6.2a part 6.VII.
- All patients will have a pre op wash with specified detergent on the morning of any surgical intervention as per paediatric department practice to reduce post operative infections.
- New policy - Patients with *M abscessus* will be kept in isolation on the ward.

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 room has 5 separated areas, 2 primary classrooms and 3 secondary classrooms.
- 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.
- 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
- *Mycobacteria abscessus*
- Multi-resistant *Pseudomonas aeruginosa*
- Respiratory viruses e.g. RSV or Influenza

The following organisms are not of particular concern –

- *Stenotrophomonas maltophilia.* 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.
- Non-tuberculous mycobacteria (NTM) – that is NOT abscessus.

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, but are not routinely requested.

Bactroban (mupirocin) nasal ointment may eliminate the organism but recolonisation frequently occurs. In the event of an outbreak, staff with direct patient contact will be screened on the recommendation of the Infection Prevention and Control Team. Such screens will include nose and any skin lesions, particularly those on the hands. Screens will be coordinated by the Occupational Health Department. MRSA positive staff will be given appropriate treatment.

We would suggest though that GPs are asked to 'surface treat' (chlorhexidine and mupirocin) the child's family (parents & siblings). It is also helpful if the child's clothes and bedding are cleaned in a 60°C. wash during the eradication period.

Children with Burkholderia species and MRSA do not attend the CF clinics and like all our CF patients, do not mix with other CF children in the hospital school and play room. These patients will attend clinic on the 2nd Friday of each even month (Feb, April, June, Aug, Oct, Dec). Patients with MRSA will be booked into earlier time slots and those with *B Cepacia* having later time slots. Due to the adult *B cepacia* clinic being held downstairs, patients will be advised to come in via Fulham Road entrance and go straight up the stairs and through physiotherapy into clinic. The HCA/Nurse will take prescriptions down to pharmacy so they do not mix with patients waiting downstairs.

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.

- A separate room is available for patients to be seen by the clinical psychologist in the outpatient department if necessary.

- 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.

- We are piloting a re-organisation of the way we do annual assessments. It is hoped in the near future to have most of the annual assessments done outside of the general clinics in the cubicles on our Sleep Unit, on Tuesdays and Thursdays.

5. Making the diagnosis

Since October 2007, newborn screening for CF has been in place throughout the whole of the UK (1st July 2007 for those born in our region). At our centre, the majority of new diagnoses are now through this route. 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 specialist centre and the screening pathway initiated.

The CF Nurse Specialist liaises with the baby's Health Visitor to discuss the result and arrange a joint visit to the family. This takes place within 5 working days on a Monday or Wednesday afternoon, enabling the sweat test to be performed the following day on a Tuesday or Thursday morning. The Health Visitor is requested by RBH not to contact the family until 9 am on the day of the visit, to arrange the appointment with them, so we do not prolong the waiting time and anxiety. The HV will be briefed by the nurse specialist to explain to the family that a nurse from the hospital will accompany them regarding part of the new born screening results and that they suggest both parents may wish to be present at the visit.

In the home it is explained that CF is likely, but that a sweat test is required and an appointment has been arranged at the Royal Brompton the following day. A sweat test is performed by one of the CF nurses specialists, which is mandatory (even if two genes have been identified), to rule out any possibility that the screening sample has 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 Consultant will take a full history, carry out a full examination and answer the parents' questions. 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 clearly suggestive of pancreatic insufficiency. A sample will be collected for stool elastase or parents are given a pot to send back.

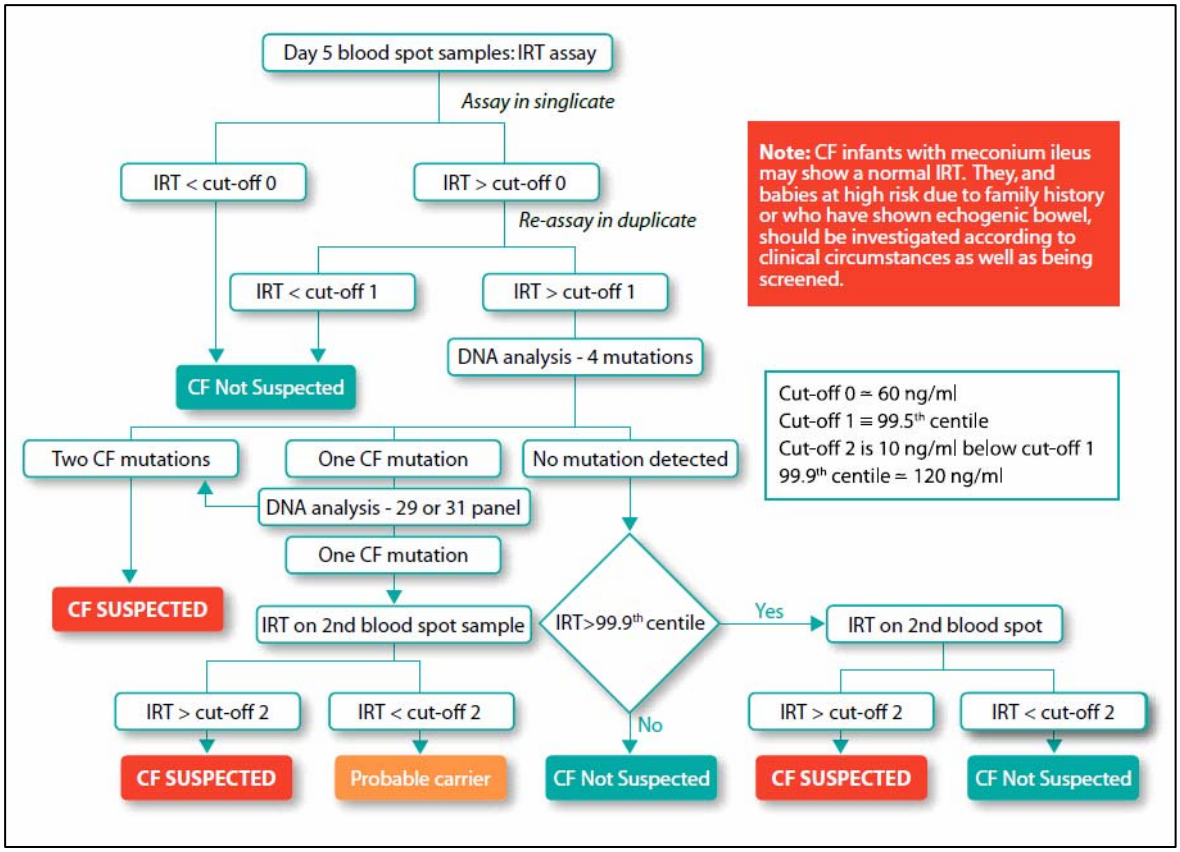
The child's GP will be informed by the consultant or nurse specialist once the diagnosis of CF is confirmed and in some cases a shared care consultant is also contacted.

A two day educational admission will be arranged for the week after diagnosis. Families are usually admitted to a cubicle in the Sleep Unit, and may go home overnight if they wish. A timetable is pre-arranged to ensure that each member of the MDT has an allocated slot in which to teach the family about their role within CF. They will meet with the consultant, nurse specialist, home care nurse, dietician, physiotherapist, clinical psychologist, pharmacist

and family liaison officer. The consultant, dietician, nurse specialist and physiotherapist meet with the family on both days to answer any questions that may have arisen.

Medication and physiotherapy are started during the admission.

After the two day admission the home care nurse visits the family the next week to offer support and go over what was taught during the admission. They review medications, physiotherapy and any problems that have arisen. The child is then seen in clinic the following week. These appointments are made during the two day admission.



Older siblings of babies diagnosed by screening will have a sweat test; usually the parents are keen for this to be done soon to allay their worries. 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, or arrange for the local hospital to do it.

5.2 Clinical presentation

This has become rarer now newborn screening is well established. 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 may 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, electrolyte disturbance suggestive of Pseudo-Bartter's syndrome 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, and analysis can be reliably performed on small 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^- <30 mmol/l;
Needs repeating	Cl^- 30 to 60 mmol/l (although in infants, this is still highly likely to be CF).
CF confirmed	Cl^- >60 mmol/l.

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 from different limbs. 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 Prof 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.

5.4 Genetic analysis

There are currently at least 1900 identified mutations in the *CFTR* gene, although not all of them are definitely associated with the clinical picture of CF. Mutations fall into different classes (I-VI), with commonest in the Caucasian population being a class II mutation, F508del (formerly) ΔF508. Nomenclature has changed recently (see appendix XI).

The CFTR2 website provides excellent data on gene mutations and their expected effects. See www.cftr2.org.

Reasons for full genotyping include the following:

- Any child diagnosed with CF:
  - facilitates screening for other family members.
  - allows prenatal diagnosis of future pregnancies.
- Since the advent of the first mutation-specific therapy ivacaftor, and on-going clinical trials of other small molecule CFTR-modulators, all CF patients MUST be genotyped. Full gene sequencing should be carried out when there is diagnostic doubt (especially in ethnic minorities).
- 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 for diagnosis rather than genetic analysis. The latter would detect carriers, which is something that should be postponed until the sibling is old enough to decide whether they wish to know their carrier status (usually mid teens and older).
- To aid confirmation of diagnosis in case of borderline sweat test.

Based on current knowledge, genotype analysis should not be used to guide prognosis in an individual child, except rarely (and very 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 include the commonest 50 mutations (which is standard at our genetic referral lab, Kennedy-Galton and costs £156).

Clearly 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. Full gene sequencing can be performed if specifically requested but is expensive (in the order of £600) and time-consuming and therefore not done routinely, for example in the case of a clear-cut biochemical diagnosis. Should mutation-specific drugs become available for mutations which are not on current diagnostic panels, this will need re-addressing. Samples should be sent to the Kennedy Galton Centre (KGC, see below); they now perform extended analysis so we no longer send samples to Manchester.

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

5.5 What happens when newborn screening results are not clear cut?

There are two scenarios when making a diagnosis after a positive NBS is less easy. There is currently no clear global or national consensus on further investigation/ management of these babies. A Delphi consensus process is underway in UK. Until guidelines are available, our management will be as follows:

1. **Borderline sweat test (30-60 mmol/L) in the presence of zero or one gene mutation**:
    a. We would say to the parents that we can not be certain for the moment, but it is likely this is CF and for the time being it is safest to treat the child as such.
    b. Request full *CFTR* sequencing *without delay.*
    c. Pancreatic insufficiency is less common in this group, but if present would make CF diagnosis highly likely.
    d. Follow up should be as for confirmed CF including regular appointments in CF clinic, bronchoscopy at 3 months old, and annual flu vaccine when over 6 months of age.
    e. Discuss with Prof Jane Davies who will likely perform nasal PD testing at the time of bronchoscopy.
    f. It is a *consultant decision* whether the child is put on CF Registry immediately.

2. **Normal sweat test in the presence of 2 mutations, at least one of which is of uncertain significance** (significance of mutation can be looked up on CFTR2 website on ww.cftr2.org currently available for commonest mutations, but database will grow):
    a. There are a number of mutations in this uncertain category. Most common one leading to this scenario is R117H/7T (if R117H is reported, always make sure the 7T/5T variant is included, otherwise *check with lab*).
        - R117H/**5T** leads to low levels of CFTR function and is considered a diagnostic mutation;
        - R117H/**7T** leads to variable amounts and is so commonly found in non-CF populations in combination with F508del, that this is not completely diagnostic. Some patients with these mutations will have CF, usually pancreatic sufficient, and others will not.
        - **9T** is almost never seen associated with R117H, so if lab report says F508del/ R117H and 9T/5T, the R117H and the 5T are together, (sometimes termed *in cis),* and the 9T can be ignored. The child therefore has the diagnostic 5T mutation.
    b. Be open about the diagnostic dilemma with the parents; it will be difficult for them, but is better than wrongly assigning a diagnosis and committing to a lifetime of treatment.
    c. Data from US/ Canada suggest that repeating sweat tests at 6 monthly intervals for the first few years of life will identify those in whom Cl^- increases into the borderline range, and who are more at risk of CF-related problems.
    d. Refer all such babies to Prof Jane Davies, who will talk further with families and follow them in her respiratory clinic with cough swabs and sweat tests in addition to monitoring growth. Parents will be taught physiotherapy, although will not be asked to do this routinely; this will change if respiratory symptoms or positive cultures appear. Babies will be transferred into CF clinic if evolution becomes suggestive of CF.
    e. Bronchoscopy will probably not be performed at the standard time although can be considered at any time.
    f. Nasal PD is likely to be normal in these cases although should be considered if a bronchoscopy is planned.
    g. Do not enter onto national CF registry (Port CF) until diagnostic dilemma is resolved.

5.6 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, F508del/-, 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 would be 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 F508del homozygous 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.

5.7 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 Mr Yacoub Khalaf at Guy's and St Thomas' Hospital Centre for Preimplantation Genetic Diagnosis.

Their website states the criteria for starting PGD treatment -

- You are under the age of 39 for women;
- You complete and return our questionnaires;
- You are living together in a stable relationship;
- (For women) your hormone levels are within a range that suggests that your ovaries will respond to treatment;
- an accurate test is available and there is a license from the HFEA;
- the PGD team agrees that you are suitable for treatment;
- there are no concerns about the welfare of any child conceived using our treatment; and
- Funding is available– either from the NHS or yourselves if you choose to pay for your own treatment. Private costs are £8000 per cycle plus drug costs (£1000-2000).

There may be an issue with CCGs agreeing to pay for the procedure. Referral forms are downloaded from www.pgd.org.uk and sent to -

Centre for Preimplantation Genetic Diagnosis
11th Floor, Tower Wing
Guy's Hospital
Great Maze Pond
London SE1 9RT

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

5.8 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

These are sent by our biochemistry lab to Birmingham. For newborn screened babies, the lab will prioritise samples to try to get the result back in 4 days, so that it will be ready for when the parents come in for their Education Visit.

- **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 Prof Jane Davies (via PA, Gina Rivellini, g.rivellini@imperial.ac.uk, 0207 594 7980), who runs a specialised nasal PD clinic monthly.

5.9 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 around 3 months of age, or 6-8 weeks after a late 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; 1 aliquot into lingula. 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. H_2-blockers and proton-pump inhibitors must be stopped 72 hours prior to admission, unless there is a very clear contraindication to doing so (*consultant decision*).

3. Other tests

- We are not doing a routine CXR pre-bronchoscopy but this will be a subject of a clinical audit.
- Consider whether overnight O_2 / CO_2 monitoring might be needed.
- Annual review bloods are taken under the GA. Ensure that blood has been sent for CF genotyping if necessary.
- 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

A chest exacerbation is a serious adverse event. Around 30% never recover their previous spirometry, and multiple exacerbations are associated with an accelerated decline in lung function. A rapid and focussed response is essential. 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, but tell them to ring back if Appointments will not give them an appointment. 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:

- Increased cough, and in particular a new or increased 'wet' cough should always be taken seriously.
- Adverse changes in sputum production (volume, colour, consistency).
- Haemoptysis.
- 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 (unless the child is obviously very unwell); 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. co-amoxiclav) 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 & specific organisms

1. Introduction – some principles

- We have adopted the antibiotic policy (including dosing) that we used for several years, as part of the LCFC 'Early detection of lung disease in newborn screened infants with CF' study.

- Note that if a 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.

- **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 11). 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 regimen. 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 11.1d for dose banding when using CIVAS, and remember to try if at all possible to prescribe antibiotics in a timely manner so that CIVAS can be used.

2. Viral colds

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.

i. If on co-amoxiclav prophylaxis, give treatment dose (i.e. double prophylactic dose co-amoxiclav preparation or if using tablets see drug formulary) for minimum of 2 weeks (see para iv).

ii. If on flucloxacillin prophylaxis - **stop it**. Give treatment dose co-amoxiclav for minimum of 2 weeks (see para iv).

iii. If on no prophylaxis, you must prescribe an antibiotic, which will cover *S aureus* and *H influenzae*. 1st choice is treatment dose co-amoxiclav; acceptable alternatives would be a macrolide (clarithromycin or azithromycin), although microbial resistance is a concern. 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.

iv. We have traditionally used these oral antibiotics for 4 weeks. We are now saying that they must be given for **a minimum of 2 weeks, but carried on for at least 1 week once the child is symptom-free.** So if for example, the child is completely well after the 1st week, then they can stop the antibiotics at 2 weeks. If it takes 2 weeks to become symptom free, the antibiotics can be stopped at 3 weeks. If however the child is not symptom free at 2 weeks, the parents must contact the CF nurse specialist for assessment.

v. It is important to differentiate [1] the child with a cold who gets better, and then has another cold soon after; for them repeated courses of oral antibiotics are appropriate (especially in the younger children during winter); from [2] the child given repeated courses of antibiotics, who does not get better, and who needs IV antibiotics instead.

vi. Oral ciprofloxacin for **2-3 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.

vii. The same is true for chloramphenicol which is very expensive in the UK. Co-trimoxazole is also used, but concerns about the rare complication of bone marrow suppression remain.

3. Surveillance respiratory cultures

Cough swabs/sputum must be sent every time a child is seen in clinic, the ward or at home. Also culture sputum if produced 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, and also when previously cultured. Culture of cough swabs for NTM is **not** useful. Remember to write 'CF' as the diagnosis so the laboratory put up the cultures to the panel of antipseudomonal antibiotics.

Positive surveillance cultures. If a child is known to be chronically infected with a particular organism (3 positive samples in the last year), and the child is well and asymptomatic, a positive routine clinic swab is not necessarily treated, although often will be. The decision not to treat MUST be discussed with the Consultant.

4. Treatment of unknown organisms

- Check previous cultures i.e. is the child chronically infected with an organism.
- Consider whether it is a viral exacerbation.
- Ensure cough swab/sputum collected for culture.

Oral treatment for mild exacerbation –

- Oral co-amoxiclav for minimum of 2 weeks, but for at least 1 week after the child is symptom-free (see above, 2.iv for details)
- Consider oral azithromycin 10 days.

- Consider oral ciprofloxacin 14 d especially if PsA grown in past.
- If severe, admit for IV antibiotics (see below).
- If the child is not symptom-free at 2 weeks, the CF Unit must be contacted by the parents.

For any gram-negative organism we must have full identification & extended sensitivities. Sometimes it turns out to be a *Pseudomonas* (not *aeruginosa*) and it is not enough to accept a report that says 'coliforms' or 'gram-negative bacilli' for example, from a local hospital. Ask the laboratory to send the strain for typing to the Public Health England Laboratory at Colindale (see appendix XIII for contact details).

5. Intravenous antibiotics – principles for unknown organism

i. **Choice of intravenous antibiotics.** This may depend on previous sputum results.

- *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.

- *Chronic infection with P aeruginosa* – ceftazidime & tobramycin is 1st line unless previous sensitivities suggest otherwise. We routinely add high dose 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.

ii. **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 11.1d).

6. Treatment of specific organisms

- A positive culture result will guide choice of antibiotic treatment, although the evidence that culture results predict treatment is weak. Do not change antibiotic therapy which is working just because of a culture result.
- **First** isolation of an organism is always treated.

I. *Staphylococcus aureus*

Ia. Prophylaxis

The question of staphylococcal prophylaxis is based on a few studies only and evidence for benefit is weak. However it is our policy to start it in all newborn screened children, 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. It may be necessary to switch to co-amoxiclav, but **we are reducing our use of this antibiotic as a prophylactic agent**. 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 3 years, flucloxacillin (or co-amoxiclav) prophylaxis should be reviewed, and only continued if *S aureus* is repeatedly cultured, in which case the possible reasons for this (e.g. non-adherence) need to be considered. **The default therefore will be to stop staphylococcal prophylaxis at 3 years of age** (in line with CF Trust national guideline). 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.*

Ib. Exacerbations

- If already on flucloxacillin prophylaxis, give three times a day treatment dose for **4 weeks** if *S aureus* is isolated and thought to be cause of the exacerbation.

Ic. First isolation

- *In a well child* (clinical judgment) we use oral co-amoxiclav for **4 weeks**.
- *In an unwell child* admit for IVABs. Use Meropenem + Tobramycin for 14 days as 1st line with high dose oral flucloxacillin; or Teicoplanin + Tobramycin for 14 days as 2nd line.

Id. Re-growths

- *Re-growth less than 6 months* from 1st growth - oral flucloxacillin three times a day treatment dose for **4 weeks**.
- *Re-growth after more than 6 months* from 1st growth - treat as for 1st growth (see above).
- *Further re-growth within 6 months* - Two oral anti-staphylococcal antibiotics for **4 weeks**.

Ie. Chronic infection

- If there are more than 2 isolates of *S aureus* in a year, give prophylaxis with flucloxacillin as above (remember under 2s will be on flucloxacillin anyway).

- For those repeatedly culturing *Staph aureus* despite regular high dose flucloxacillin, consider other treatments, especially in older children. For example co-amoxiclav, fusidic acid or even rifampicin if this persists.

- **Use of linezolid – see below.**

II. *Haemophilus influenzae*

IIa. First isolation

- *In a relatively well child* (clinical judgment) we use oral co-amoxiclav for **4 weeks.** This 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*

- *In an unwell child* admit for IVABs. Use Ceftazidime + Tobramycin for 14 days.

IIb. Re-growths

- *Regrowth less than 6 months* from 1st growth - oral co-amoxiclav for **4 weeks**
- *Re-growth after more than 6 months* from 1st growth - treat as for 1st growth
- *Further re-growth within 6 months* - clarithromycin for 14-28 days (assuming not resistant).

IIc. Chronic infection

- If ≥ 2 isolates of *H influenzae* in a year, consider co-amoxiclav prophylaxis, although evidence is even less secure and we are reducing our use of this drug as a prophylactic agent. 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, unless no other option is available. Watch out for *H influenzae* macrolide resistance as well. **Cephalosporins are not to be used** for long term prophylaxis because of worries about increased *Pseudomonas* isolation.

III. *Pseudomonas aeruginosa*

If the report indicates the organism is **resistant** to colistin, this may well be a *Burkholderia* species not *Pseudomonas*, and the sample must be sent to the Public Health England Laboratory at Colindale (see appendix XIII for contact details).

IIIa. First isolation in newborn screened child - in 1st 3 months of life

- If grown on cough swab before their initial bronchoscopy we will carry out standard eradication -
  - **3 weeks** oral ciprofloxacin (or dual therapy intravenous antibiotics if unwell)
  - PLUS **3 months** nebulised colistin twice daily.

  We will then defer the usual 3 month bronchoscopy until after eradication treatment, to check that it has been successful.

- If the 1st *Pseudomonas aeruginosa* was grown on the 3 month BAL only, and not isolated on cough swab done on same day, we will usually 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 assume we cannot rely on a clear cough swab.

IIIb. First isolation in older child

- **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 do not routinely use gentamicin nebuliser (with colistin) unless there are also significant problems with *S aureus*.

Note – check if child suitable for TORPEDO study when PsA first isolated. Discuss with Prof Davies or Prof Bush.

IIIc. Re-growth during the initial 3 month treatment period (whilst still on colistin)

- **In a well child,** give a further 3 weeks ciprofloxacin. Switch colistin to nebulised tobramycin for 1 month then back to colistin. 3 month nebuliser course starts from date of latest positive isolation. Consider IV therapy also.

- **In an unwell child,** give IV Tobramycin and Ceftazidime for 2 weeks. Switch colistin to nebulised tobramycin for 1 month then back to colistin. 3 month nebuliser course starts from date of latest positive isolation.

- Or if IV antibiotics already given at 1st isolation, can give 3 weeks ciprofloxacin and switch colistin to nebulised tobramycin for 1 month then back to colistin. 3 month nebuliser course starts from date of latest positive isolation. A 2nd IVAB course may be appropriate.

- further 3 months nebulised colistin

IIId. Regrowth at end of 3 weeks ciprofloxacin / 3 months nebulised colistin course

- Admit for 2 weeks of IV ceftazidime & tobramycin

- And either: 3 further month's nebulised colistin.
  Or 3 further months of alternating nebulised colistin / tobramycin.

IIIe. Subsequent regrowths

- Isolations of *P aeruginosa* after six months or more of clear cultures are **always** treated. We assume this is a new isolate so attempt re-eradication with 3 weeks oral ciprofloxacin. ALSO they must restart long term nebulised colistin twice daily if they were not taking it already. If they were on colistin still when they had the new growth, consider switching to nebulised tobramycin.

- If ciprofloxacin-resistant, we use a 1 month course of nebulised tobramycin, which can be extended to 6 months of alternating tobramycin/colistin (*Consultant decision*). If 1 month given, we then follow with to 6 months nebulised colistin.

- If unwell, a 2-week course of dual therapy intravenous antibiotics are given.

- 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.

- 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.

- For 2nd and subsequent isolates unless there is a long interval between isolates (discuss with Consultant) - lifelong twice daily nebulised antibiotics, using colistin.

IIIf. Choice of IV antibiotics for *Pseudomonas aeruginosa*

- Check for drug allergies.
- 1st line is ceftazidime + tobramycin.
- 2nd line is meropenem + tobramycin (this may be 1st line if Staph aureus also grown).
- The parents/patient often knows which combination has worked best in the past and it is often worth going with their choice (unless there is a good reason not to).
- Known antibiotic sensitivities on last sputum/cough swab PsA culture not always relevant.
- Subsequent choices (not in particular order) – aztreonam, colistin, amikacin, timentin (see formulary). We rarely use tazocin because of allergy including cross reactions.
- I**ntravenous fosfomycin** is relatively new**.** *Consultant decision* only, for very resistant *PsA* in children 12 years and above and adults. It is an unlicensed product in the UK which has to be imported.
- We never use IV gentamicin (it is not in our formulary).
- Check whether patient allowed aminoglycosides (known renal, hearing problems).

IIIg. 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:

Tobramycin	10 mg/kg once daily over 30 minutes
Amikacin	30 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
- Intercurrent diarrhoea and/or vomiting
- DIOS
- Other nephrotoxic drugs e.g., ibuprofen.

IIIh. Chronic PsA infection

- **This is defined** for analysis purposes by the Leeds criteria:
  - Never: never cultured
  - Free: cultured previously but not in last year
  - Intermittent: cultured in < 50% of samples in past year (must be 4 samples per year)
  - Chronic: cultured in > 50% of samples

- 1st line treatment for chronic infection is long term inhaled colistin.

For children chronically isolating *PsA* and doing badly, consider rotating tobramycin and colistin nebulisers. Tobramycin should be considered if, despite continued therapy and good adherence to treatment, lung function continues to decline or there is a requirement for more than one course of IV antibiotics in the preceding year. We use Bramitob or TOBI. *Consultant decision* to start inhaled tobramycin.

- **Aztreonam lysine** for inhalation (Cayston) is licensed for children >6 years old, and is routinely funded for the treatment of appropriate adults and children with CF in accordance with national clinical criteria. A stepwise approach is recommended, colomycin remains 1st line, alternating Tobramycin/colistin remains 2nd line treatment. Aztreonam is our 3rd line.

  Aztreonam lysine may be considered if there is still progressive loss of lung function (defined as greater than 2% per year decline in FEV_1 as % of predicted) or there is continued need for IV therapy for exacerbations i.e., more than 2 per year despite therapy with an alternating regimen of tobramycin and colistin. This may be prescribed either alternating with colistin or tobramycin depending on the clinical response to those medications previously.

- Patients should be recommended not to expose themselves to loud noises *e.g.* loud music played through headphones / earbuds, when receiving intravenous aminoglycosides.

- 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. See section 6.15b.

- **Long term intravenous colistin**. Occasionally we have used long term twice daily IV colistin 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

IIIi. Dry powder antibiotic inhalers (see also section 6.15d).

- It is important to note that even if the child has been safely using a nebulised antibiotic, if it is planned to switch to a dry powder, the first dose must be given under supervision to check for bronchoconstriction (book challenge with Physiotherapy Dept. using their request form). It is essential to check the child knows how to use the device, as with all inhaled medication. See section 6.15b.

- **TOBI Podhaler**
  Tobramycin given by the TOBI podhaler has been shown to be non-inferior to TOBI™ and is of equivalent cost. It should be offered to children who are either using nebulised tobramycin or are being started on it. It is not the first-line treatment for *Pseudomonas aeruginosa* infection; the existence of this device does not alter our choice of inhaled medication. Like nebulised antibiotics, the inhaled is excluded from the PbR tariff, so we are reimbursed if we prescribe it. It is approved by commissioners as long as cost is not higher than its nebulised equivalent. The first month will be prescribed in clinic and

supplied by our pharmacy; subsequently it will be supplied by the hospital's home care delivery service.

- **Colobreathe turbospin**
  Colobreathe to deliver colistin is now available, and has been shown to be equivalent in efficacy to nebulised TOBI™. At the moment we are required to use as per NICE guidance in order for the Trust to be reimbursed, so this should be discussed with a Consultant first. The guidance is that Colobreathe can be used if the child will clinically benefit from continued colistin but does not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered**.** This is difficult, because in general we do not have problems with patients not tolerating colistin nebulisers. The device would be attractive potentially to improve compliance. This guidance may be updated and clarified in the near future, which would change our recommendations. The first month will be prescribed in clinic and supplied by our pharmacy; subsequently it will be supplied by the hospital's home care delivery service.

IV. MRSA

- For 1st isolation in sputum/cough swab, we attempt eradication as there are data showing MRSA adversely effects lung function. We treat for **3 months** with 2 oral agents, usually rifampicin plus fusidic acid or trimethoprim. Beware of hepatic toxicity.
- Prophylactic flucloxacillin or co-amoxiclav should be stopped in patients with MRSA until the MRSA is successfully eradicated.
- Nebulised vancomycin can also be considered.
- 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 (see below), available orally and IV, when traditional agents fail (*consultant decision*).
- Check current Hospital Policy on the intranet; also remember surface decontamination protocols.

Linezolid. Is an oxazolidinone, and 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.

V. *Burkholderia cepacia* complex

The *Burkholderia cepacia* complex consists of 9 well-established genomic species called genomovars: *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. vietnamiensis*, *B. stabilis*, *B. ambifaria*, *B. dolosa*, *B. anthina*, and *B. pyrrocinia;* recently *B. pseudomultivorans* has been described as a new species. Although previously commonly referred to by genomovar number, these names should now be used in preference (*e.g*. old genomovar 3 is *B. cenocepacia*) and only the first of these species should be referred to as *B. cepacia.* Culture requires specific, selective media and every attempt should be made to fully identify strains at the molecular level; misidentification is common. Several species have been reported in epidemics and incidence has decreased since the widespread adoption of strict segregation and cross-infection control measures. Reports have confirmed some strains as conferring an adverse prognosis (*e.g. B. multivorans*, *B. cenocepacia* and *B. dolosa*) and *B. cenocepacia* is an exclusion criteria for many transplant programmes because of a clear survival disadvantage post-surgery.

- If detected at shared care hospital, please notify Brompton for advice. Ask the laboratory to send the strain for typing to the Public Health England Laboratory at Colindale (see appendix XIII for contact details). The local diagnosis may be wrong, because really experienced, CF specialist laboratories are needed to type unusual organisms. This is true also for any other unusual and rare organisms.

- Patients who become infected with BCC do not come to usual CF clinic, but are now being seen in clinics held on the 2nd Friday of the month in even numbered months (Feb/Apr/June/Aug/Oct/Dec). If they are on the ward, they are kept isolated in a cubicle for the whole admission.

- **Eradication** -: this must be discussed with the consultant. We attempt to eradicate 1st isolation with IV antibiotics, and choice will depend on sensitivities, and may include meropenem, timentin, temocillin.

- **Chronic suppressive therapy** - As the *B. cepacia* complex bacteria are uniformly resistant to colistin the choice will be between nebulised ceftazidime, meropenem, tobramycin, aztreonam lysine or temocillin. Long term oral therapy may be considered including doxycycline.

- We may also consider oral trimethoprim or co-trimoxazole for minor symptoms in a chronically infected patient.

VI. *Stenotrophomonas maltophilia*

- This: usually clears spontaneously and is frequently not pathogenic; however in some patients it is associated with new symptoms and changes in lung function. 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).

VII. 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 often there as commensals and have no significant effect on respiratory function or nutritional status. The exception is *M abscessus*, which has increasingly been found to cause significant lung disease.

A single isolate is NEVER treated, and even a child with multiple isolates has a 50% chance of not being infected. However treatment is increasingly required (*consultant decision*). It is important to ensure symptoms are not wrongly attributed to NTM, and other more easily causes have been treated. Antibiotic sensitivity testing is critical. **See appendix II for detailed antibiotic policy** on treatment of NTM (joint with adult RBH unit).

Cough swabs must not be sent for NTM culture as our study shows they are always negative. We culture sputum or BAL specifically for NTM -

- annual assessment visit
- in a child who is unwell but culture-negative
- any child having a bronchoalveolar lavage
- on admission for an exacerbation
- when previously cultured.

Patients with *M abscessus* will be kept in isolation on the ward, and seen at the very end of clinic.

Patients are considered free of *M abscessus* when they have had 4 negative samples over a year from the 1st negative sample, when the patient is not receiving treatment. This means they can not be considered negative until at least 1 year off treatment.

If it was only isolated on a BAL in a non-sputum producing child, then if induced sputum can not be obtained, the child will need 2 x BALs in a year to be negative. The guidance suggests one negative BAL off treatment is sufficient, but we are being even more cautious.

VIII. *Achromobacter xylosoxidans*

- There is a dearth of evidence, so always discuss with Consultant.
- For first isolation we attempt eradication and may use intravenous antibiotics if the child is unwell. This usually includes IV colistin.
- If intravenous therapy is given, it is probably wise to give nebulised colistin as well for 3 months at least, possibly also with an oral antibiotic, if the *Achromobacter* is sensitive to one suitable for medium term use.
- Otherwise we may use oral co-amoxiclav for 1 month and nebulised colistin for 3 months. Oral alternatives are co-trimoxazole or minocycline (if age > 12 years), depending on the sensitivities.
- For established chronic infection nebulised colistin is used long term, with nebulised meropenem as 2nd line.

IX. *Serratia marcescens*

There is very little in literature in CF patients and unclear what to do with it (adult unit unsure also but they tend to attempt eradication with oral followed by IV antibiotics). We do see a few cases and decide on an individual basis i.e. if child unwell and this is only isolate, we would tend to treat. Check sensitivities of isolated organism. Otherwise we may just repeat cultures and watch progress.

X. Candida

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. Alternative is miconazole. There are controversial data suggesting that *Candida* is a marker of poor prognosis, but our view is that it is a marker only, and not causative. We would treat it if isolated in BAL.

XI. Influenza

NICE guidelines have changed since our last Guidelines. They now state that oseltamivir and zanamivir are recommended to prevent flu if **all** of the following apply:

- The amount of flu virus going around is enough that if someone has a flu-like illness it is likely that it has been caused by the flu virus
- The person is in at 'at risk' group (i.e. all our CF patients)
- The person had been in contact with someone with a flu-like illness and can start treatment within 36 hours (for zanamivir) or within 48 hours (oseltamivir).

Hence if our patients are immunised against influenza as they should have been, then they do not need Oseltamivir or zanamivir. If the child has not been immunised, they must be encouraged to see their GPs early for a prescription when there is a high flu incidence. 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 or sputum or viral throat swabs) should be taken for virus detection to confirm the diagnosis.

6.2b Drug allergy & desensitisation

Allergy

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 chlorphenamine (<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.

Do not attempt to restart a similar class antibiotic for at least 48 hours.

Antibiotic desensitisation (see below) 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 (usually at day 10), 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 6.2c).

Additionally any child, who has had a previous allergic reaction to an IV antibiotic, must have an epipen at home if receiving further home IV antibiotics.

Desensitisation

(Adapted from the material printed in the UK CF Trust Antibiotic Treatment for Cystic Fibrosis Guidelines, March 2009 and http://www.cysticfibrosismedicine.com).

Frequent high-dose intravenous antibiotic treatment in CF patients increases the incidence of drug-associated hypersensitivity reactions. These reactions have been reported with most of the antibiotics in regular use for patients with CF, including aminoglycosides, ß-lactams, and quinolones. The choice of antibiotics may therefore be limited by a history of previous allergic reaction and patients denied optimal treatment.

Antibiotic tolerance may be induced by following desensitisation protocols, although it should be noted that the patient will need desensitising to the drug at the start of **EVERY** treatment course and repeated during a course of therapy if more than one day's doses are omitted. Document the outcome of the desensitisation procedure in the medical notes, and if a reaction occurred, document the exact nature of the reaction.

An example of such a regimen is shown below. The principals behind this regimen can be adapted for other drugs, and if a desensitisation regimen is being considered, then please discuss with a member of the paediatric pharmacy team in advance of the patients admission:

Example Regimen

- Administration of a 10^6 times dilution of the drug followed by 6 x ten-fold increases in the concentration (starting with the least concentrated) until the therapeutic dose is given (final dose calculated using patient's weight)
- Each dilution is infused consecutively over 20 minutes.
- During the desensitisation procedure, which takes about 2–3 hours, the patient is observed for signs of allergy.
- If 7 infusions are tolerated, the therapeutic dose is continued until the course is completed.

- Example of a desensitisation regimen for final dose Ceftazidime 2g (2000 mg)
    - Ceftazidime 0.002 mg in 20 ml sodium chloride 0.9% (NaCl)
    - Ceftazidime 0.02 mg in 20 ml NaCl
    - Ceftazidime 0.2 mg in 20 ml NaCl
    - Ceftazidime 2 mg in 20 ml NaCl
    - Ceftazidime 20 mg in 20 ml NaCl
    - Ceftazidime 200 mg in 20 ml NaCl
    - Ceftazidime 2,000 mg in 20 ml NaCl.

- Adrenaline, hydrocortisone and an antihistamine should be readily available and the appropriate doses for the patient known before starting the procedure (Some patients benefit from treatment with antihistamines pre and during desensitisation)
- Facilities for full resuscitation should be close at hand.

If a reaction (anaphylaxis, wheezing, swelling, itching, urticaria) occurs during desensitisation, the procedure should be stopped and no further attempts should be made to administer that antibiotic to the patient.

Procedure at RBH

1. If a patient requires desensitisation, the paediatric pharmacy should be alerted prior to admission, with as much notice as possible.
2. Medications that require desensitising will each have an individualised regimen (produced by the paediatric pharmacy team) with instructions for preparation and administration.
3. All doses for the desensitisation regimen should be prescribed on the 'once-only' STAT side of the chart.
4. Each of the drug solutions will be administered to the patient as 20 minute infusions. Once one infusion has finished, the next one should start immediately. The entire procedure will take approximately 2-3 hours.
5. Adrenaline, Chlorphenamine and Hydrocortisone should ALWAYS be prescribed on the 'when required' side of the drug chart. They should also be drawn up and ready to administer to the patient if required. (Please refer to the latest copy of BNF-C for appropriate doses or above in allergy section).
6. If a reaction (anaphylaxis, wheezing, swelling, itching, hives) occurs during desensitisation, the procedure should be stopped and no further attempts should be made to administer that antibiotic to the patient. Please note, that some patients may feel nausea which can usually be relieved with the use of a regular anti-emetic.
7. If a reaction occurs, the reaction and its exact nature should be documented in the patient's medical notes.
8. If the patient tolerates the desensitisation regimen, the final dose should be prescribed in the drug chart (regular IV section) and should be continued for the remainder of the course.
9. If doses are omitted for more than one day, the desensitisation process will need to be repeated.

6.2c Home IV antibiotics

- Lack of bed space is not an indication for home IVABs. However if a long delay is anticipated, other solutions such as using the local hospital or home IVABs should be discussed with the on-call or named Consultant.

- 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). Likewise, each time, an assessment will be made by the Consultant and CNS as to whether Home IV therapy is the most appropriate method for that specific occasion.

- Patients should 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 the Fresenius Kabi Eclipse device (left) or Baxter Intermate device (right).

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/ physiotherapist 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.

6.2d 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 procedural anxiety or 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, and use oral e.g. ciprofloxacin instead.

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 and looked at 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 -

- **Failure to access port** - usually by less experienced personnel, and usually fine when done by one of our CNS team. If this is an issue, discuss with CNS.
- **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. VQ 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 6.9. 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, osteoporosis, and Cushing's syndrome. Exposure to chicken-pox in a child who has not yet had it, may require varicella-zoster immunoglobulin (see section 10.2 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 been proven.

We use budesonide or fluticasone but not beclometasone. 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 may include a reduction in final height (long term asthma studies suggest 1cm loss), 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. Remember the issue of adrenal suppression in those also on itraconazole. Finally, there may be an association of ICS use with acquisition of NTM.

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 (never use salmeterol or formoterol alone). We would normally use a combination inhaler (Seretide or Symbicort) to make it easier for the children.

6.4 DNase (Dornase alfa, Pulmozyme)

DNase 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

- Our new policy is to consider starting DNase for **ALL PATIENTS WHEN THEY ARE 6 YEARS OLD, whatever their lung function** (as per European CF Society recommendations). We intend it to be unusual for a child aged 6 and above to not be on it.
- For our current older patients, its use needs to be discussed. We would push strongly to start any child
    - whose FEV_1 is <85%.
    - who hardly expectorates at all but has symptoms.
    - who has persistent wheezing.
- We would consider it in preschool children if there is concern over their respiratory status.

Other indications include.

- Persistent or recurrent focal x-ray changes e.g. consolidation in a lobe or segment, when we would consider bronchoscopy with instillation under direct vision – see section 6.14. It would be expected a child like this would already be on it regularly.
- During an admission for a chest exacerbation it may be useful, and we would follow the recommendation of the physiotherapists.

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. There seems to be no clinical difference between daily and alternate days treatment. 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). The default will be to use DNase daily, but consideration can be given to alternate day therapy after 6 months in those who are well or who find the daily treatment a particular burden (6.4). 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, but it can lead to night time coughing so check in clinic after a month or so. First line timing remains the afternoon.

Involving the GP - This is an expensive drug (about £7500/year if used daily). From April 2014 we are responsible for the prescription. A new prescription will be given by our

pharmacy, and future prescriptions via the home delivery service (and we are still reimbursed).

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 often 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: an exceedingly safe drug - 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 DNase which is given a minimum of 1 hour before physiotherapy. It can though, in some cases be combined with physiotherapy. Although this reduces total drug deposition in the lungs, it improves the peripheral deposition; it also saves the patient time. It is often suggested that the dose should be increased e.g. to 5-6 mls (but not usually done in practice). If HS cannot be tolerated, lower concentrations may be considered. We use Nebusal (7% hypertonic saline) that comes in individual 4ml single dose plastic ampoules and is prescribable by GPs.

For sputum induction, which may be indicated in the CF patient over age 6 years who has a rattly cough, and is not doing well, but does not expectorate sputum spontaneously, we use 7% saline ('normal' saline is 0.9%). 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.

During an admission for a chest exacerbation it may be useful, and we would follow the recommendation of the physiotherapists.

The first line mucus clearance agent is DNase, but our data show that a third of DNase 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 ISIS study was essentially negative in CF children under 6, although in a subgroup analysis, LCI decreased in the treated group. This does not preclude the use of HS in young infants, but be aware of the weaker evidence base in this age group. 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 DNase. See also section 6.6 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 two phase 3 studies suggest that it may improve lung function in some patients with CF. A NICE review of the role of inhaled mannitol recommended its use in adults with CF. Children who do not respond to DNase 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. The large number of capsules used per dose means that this is a time-consuming therapy. All patients are pre-treated with bronchodilator 15 minutes prior to administration. As with DNase, 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 only licensed in adults 18 years and above and not currently approved by Royal Brompton & Harefield NHS Foundation Trust Medicines Management Board for use in children (Nov 2013). NHS England funding is required prior to initiation, and its use is a Consultant only decision.

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 DNase (see section 6.4) and should include those not benefiting from a 3 month trial of DNase.

Dosage: 250 mg once daily (<40kg) or 500 mg once daily (≥40kg) **three times a week** (Mon Wed Fri)

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. There are some anxieties in the literature about Azithromycin acting as a single agent NTM treatment, although examining our own data and the US study suggests no increased risk of isolating NTM in those on AZM, indeed we found that long term AZM may reduce the NTM risk.

When AZM is started, consider stopping prophylactic flucloxacillin or co-amoxiclav, unless there is a good reason to continue, ie patient is known to have macrolide-resistant organisms.

6.8 Ivacaftor

In December 2012, ivacaftor was approved by NHS England for clinical use in CF patients 6 years of age and above with at least one copy of the G551D mutation. All eligible patients in our clinic were commenced on this oral preparation, which is planned for long-term, uninterrupted use. We should be aware of younger patients, and prepare for starting treatment on or shortly after their 6th birthday. See Clinical Commissioning Policy March 2012 - www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf.

Mechanism of action

Ivacaftor (Kalydeco^{TM}) is a small molecule drug which binds to CF at the cell surface and leads the chloride channel to open (this is termed 'potentiation'). Class 3, the 'gating' mutations mean the channels are not open often enough, and when open are open for shorter time periods, and the commonest of these, G551D, is the group in which drug efficacy was originally confirmed. Phase 3 trials demonstrated significant improvements in FEV_1 (around 16-17% of baseline), reduction in exacerbations, significant weight gain, and a large drop in sweat chloride (often into the borderline, or even normal, range). The commonest CF mutation, F508del, results in CFTR protein which does not reach the cell surface and it has clearly been shown that this drug, as a single agent, is ineffective. Trials are on-going in non-G551D gating mutations and in R117H, but currently the drug is not licensed for use outside G551D.

Ivacaftor is administered twice daily at 150mg in tablet form. It is crucial that it is taken with or very shortly after a high-fat meal or snack, as otherwise absorption is poor. Tablets must not be chewed.

Side effects were minimal in trials, although rashes are common. Rises in liver function tests were observed in some patients, and although these did not differ significantly from the placebo group, monitoring has been put in place (see below). Dose reduction recommendations are available for patients with significant hepatic or renal impairment.

Drug interactions: There are some significant interactions, most importantly:

- **Azole antibiotics**: (itraconazole, voriconazole) lead to inhibition of the breakdown pathways of ivacaftor and accumulation of the drug. If co-administration is necessary, the dose of ivacaftor should be reduced; manufacturers suggest to twice weekly although this comes from modelled data, not human PK studies, and anecdotally, this may lead to loss of efficacy. Consultant advice should be sought in this event. Ivacaftor levels are not currently available, but sweat Cl^- could provide a useful surrogate for bioavailability.
- **Clarithromycin**: also leads to accumulation of the drug so suggested take ivacaftor three times a week. There is no interaction with azithromycin, so use AZM instead.
- **High dose corticosteroids**: may significantly decrease serum levels of ivacaftor and reduce efficacy.
- **Rifampicin**: will significantly reduce ivacaftor levels; co-administration not recommended.
- **St John's Wort:** as for Rifampicin.
- **Grapefruit** (or juice) and **Seville oranges** (realistically, this is only marmalade; edible oranges are all fine): should be avoided as they reduce serum levels of ivacaftor. 'Lilt' fizzy drink does contain pure grapefruit juice, but in such small quantities, it is fine

Pre and on-treatment monitoring & stopping criteria (see proforma in appendix IV).
Due to the very high cost of the drug, the Commissioners in England have mandated monitoring and have imposed stopping criteria. See www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf . Sweat test should be done within the 6 months prior to starting treatment and again at the next routine appointment (around 8 weeks).
The patients will be considered to have responded to treatment if either

a) the patient's sweat chloride test falls below 60mmol/L **OR**
b) the patient's sweat chloride test falls by at least 30%.

In cases where the baseline sweat chloride test is already below 60 mmol/L, the patient will be considered to have responded to treatment if either

a) the patient's sweat chloride test falls by at least 30% **OR**

b) the patient demonstrates a sustained absolute improvement in FEV_1 of at least 5%. In this instance FEV_1 will be compared with the baseline pre-treatment level one month and three months after starting treatment.

If these changes do not occur, compliance and issues including taking it with fat, swallowing whole, concomitant medication should be thoroughly explored. If no explanation is found, the sweat test should be repeated the following week and ivacaftor stopped if there is still an inadequate change. Experience has now shown though that clinical response does not correlate with sweat chloride changes.

- Liver function tests needs performing every 3 months for the first year but can then be done with annual assessment.

- Sweat tests are repeated annually as per commissioner's guidance.

We are also requesting a number of additional investigations including LCI and serum/ sputum research markers. Please ensure that Prof Jane Davies is informed before a new patient is commenced on treatment.

6.9 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/chest tightness 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. Note though that in some cases who do well, the IgE does not fall, so treat the patient not the IgE level. 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. It is usually for 3 months, but may be longer depending on the response. Decision to use should be discussed with the consultant, but this is increasingly our preferred option.

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; and inhaled corticosteroids can cause adrenal suppression if also on itraconazole.

Itraconazole levels
We no longer measure itraconazole levels routinely. However levels may still be indicated if there are concerns that a patient is not responding adequately to treatment; about toxicity; or if interacting drugs are introduced. Due to a change in processing methods, please note that trough levels are now necessary.

- Trough sample should be taken after patient has been taking for at least 14 days (usually taken at the last bloods prior to discharge)
- Range: parent molecule: 0.5 - 2mg/l & total of 1 - 4mg/l
- 1ml of serum into clotted blood vacutainers

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. If not consider increasing the dose first. Voriconazole should only be started with consultant approval. When given for acute ABPA, it is stopped when the steroids stop. 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). Similarly to itraconazole, adrenal suppression has been reported in patients on voriconazole also taking inhaled corticosteroids. 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

Voriconazole is expensive (~£1-3000/month) and can be prescribed by GPs (although many will not prescribe it, so we then have to send it from our home care service). Whilst it is not listed in the high cost drugs that are excluded from the CF PbR tariff, it has already been excluded from general PbR tariffs, so all hospital trusts can be reimbursed for its use.

Posaconazole is an alternative when voriconazole is not tolerated and it is critical to treat the patient with a second line agent. Blood levels can be obtained when initiating therapy. It is not licensed for children under 18 years so it is a *consultant decision* to use in older children. See formulary for dosing. *Currently not approved by our Trust's New Drugs Group for use in children, and we would need approval from NHS England for reimbursement, prior to prescribing if possible (unless required urgently).*

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). 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 on the basis of case reports; this is a *consultant decision* and funding approval will be needed prior to starting.

2. Other manifestations of aspergillus lung disease

- It is becoming increasingly clear that *Aspergillus fumigatus* causes more than ABPA, and sensitisation or persistent positive cultures are associated with a worse prognosis. Remember this in the child with repeated positive sputum cultures especially if chronically symptomatic, also in 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.

- 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.

- Mycetoma is rarely seen in CF but has been described. Suspect if halo sign in a cavity and 6-8 positive IgG ICAP. 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.

Scedosporium apiospermum

With the advent of molecular techniques, the importance of other fungi such as *Scedosporium apiospermum* is being appreciated. Scedosporium is the second commonest fungus isolated in CF respiratory secretions. Clinical implications of colonisation are poorly understood, it is usually not associated with symptoms but it has been known to cause an allergic bronchopulmonary mycosis (similar to ABPA). If treatment is considered, azoles are the drugs of choice.

6.10 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 DNase 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).
- **Oral atenolol** has been used on an anecdotal basis - *Consultant decision*, and remember even selective β-blockers can cause bronchoconstriction. Starting dose is 0.5 mg/kg once daily (max 12.5 mg OD). Dose can be titrated up if necessary.
- **Lobectomy** may be considered as a last resort.

6.11 Pneumothorax

See BTS guidelines -

http://www.brit-thoracic.org.uk/Portals/0/Guidelines/PleuralDiseaseGuidelines/Pleural%20Guideline%202010/Pleural%20disease%202010%20pneumothorax.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 BTS guidelines about flying after a pneumothorax – need to wait at least six weeks.

6.12 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 (who anecdotally are becoming rarer) 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 6.13).

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 if using high doses 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. However there is increasing evidence that steroids (oral and inhaled) increase the risk of isolating NTM so as always a consideration of risks and benefits is required.
- Consider using short acting β2 agonists, 10 puffs 3-4 times a day via a spacer.

- Consider Tiotropium inhaler – an antimuscarinic agent. Although only licensed >18 years it may still be necessary for this difficult problem in younger patients. This is a *Consultant decision*. We should use the Spiriva® Handihaler (dry powder) 18 mcg once daily. We do not use the Respimat® MDI as the product license specifically states not to be used in CF.
- Consider slow release theophyllines e.g. Slophyllin – see BNFc for doses.
- Consider also IV aminophylline for an in-patient with severe wheezing (use standard acute asthma doses).
- 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 as a single dose 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. 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 **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, especially the first dose, can activate complement with impressive side effects (severe headache, flushing etc.).

- **Azithromycin.** No objective evidence in this situation 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 up to 20 mg/m^2/week would be considered if no benefit occurs at 10 mg/m^2/week. 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. 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. Similarly to itraconazole, adrenal suppression has been reported in patients on voriconazole also taking inhaled corticosteroids.

- **IV liposomal amphotericin** (Ambisome). Consider with resistant ABPA (see section 6.9) 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 colistin, or aminoglycosides** (risk of renal failure).

- **Omalizumab** (Xolair) (see ABPA section 6.9). 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, and has been occasionally very successful in our unit. Subcutaneous injection every 2 to 4 weeks depending on IgE level. As unlicensed for this indication, funding must be confirmed before starting treatment.

6.13 'Challenging CF' protocol

Introduction Clearly some of this protocol will have already been done as part of the child's routine clinical care. We activate this protocol if we are 'stuck' despite routine measures; this replaces the decisions e.g. to admit for a bronchoscopy, usually taken in a busy clinic or at the weekly post-clinic MDT meeting. This protocol is based on what we do successfully with our MDT approach to severe asthma.

Definitions (which are guides, not prescriptive)

a. Any child whose spirometry is worse than -2 Z-scores.
b. Any child who receives $\geq$ 3 courses of intravenous antibiotics annually (whether planned electively or unplanned).
c. Any child requiring home oxygen (almost invariably will have been assessed in the protocol long before this stage).
d. Any child in 'nutritional failure' –BMI < 2 Z scores below the mean; drop in weight or BMI centiles by 10% over a year.
e. Any child with a severe CF pulmonary complication.
    - Massive haemoptysis.
    - Pneumothorax.
    - Therapy resistant ABPA or other cause of severe steroid dependency.
f. Any child whose self or parent-reported symptoms are significantly different to what a clinician would expect (either over- or under-estimated).
g. Any child in whom there is refusal or extreme reluctance to give prescribed treatment by the carers.

What are the likely causes?

1. Non-adherence to therapy - we need to obtain objective data.
    - obtain record of GP and hospital (RBH and local) prescriptions;
    - 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 supposed to know;
    - down-loading data from nebulisers about usage;
    - blood levels if on prednisolone or theophylline. Consider also if on itraconazole and voriconazole.
2. Adverse environment
    - passive or active smoking (salivary/urinary cotinine)
    - allergen exposure (RAST and skin tests)
    - home environment, including nebuliser cleanliness (very important if ABPA the issue).
3. Significant co-morbidity – upper airway disease (ENT evaluation including imaging where appropriate), gastro-oesophageal reflux (pH study, GI referral if any doubt)
4. Social challenges - parenting/other. Needs sensitive assessment to look at family's strengths and challenges.
5. Nutritional failure (especially if relatively good pulmonary function)
    - *Impaired glucose metabolism* - see Nicola Bridges or Saji Alexander to assess need for CGMS, OGTT, home glucose monitoring (see section 8.1).
    - *Malabsorption* - basic GI screen including food diary, faecal fat microscopy, coeliac screen, ESR, urinary electrolytes, and GI referral if still an issue.
    - *Gastro-oesophageal reflux* (pH study, GI referral if any doubt)

6. Psychological issues which are of course part of non-adherence, but there is much more to it than this – full assessment; should include those who 'overcall' the child's symptoms also.
7. 'Bad lung disease' of which there are two main types which need to be separated by investigations (below)

    - 'Distal and dry' – the child who has distal airway disease with air trapping on inspiratory and expiratory CT scans, non-sputum producer and dry airways on bronchoscopy. MUST exclude reflux. Need to explore systematically acute bronchodilator reversibility, pulsed methyl prednisolone, and others – intravenous immunoglobulin has been our first line, but may be a supply issue in the future. See section 6.12.

    - 'Pan-airway and productive' – the child who has bad proximal bronchiectasis and marked purulent airway secretions. Make sure we know everything about what is growing in the airway (including anaerobes, NTM, unusual gram negative rods, consider getting 16sRNA studies for the real oddities) by BAL (consider induced sputum regularly also), then rotating nebulised antibiotics, 3 monthly intravenous antibiotics, long term macrolides, DNase, hypertonic saline, different physiotherapy techniques

Protocol:
Pre-protocol: Our severe asthma experience shows that we can obtain important information at a pre-screen, without time-consuming home visits. So obtain prescription records and have uptake assessed by Pharmacy; urine or salivary cotinine; skin prick tests for any allergic component.
Step 1: Multidisciplinary assessment but at a planned separate visit, not part of the busy routine clinic. See nurse specialist, physiotherapists, dietician, psychologist, and pharmacist. Tests will include RAST and/or skin prick tests, salivary cotinine if not already done. Refer to ENT outpatients. Ideally get all this done in one admittedly tiring day. Home visit jointly by nurse specialist and physiotherapist; the team feel this may need to be done on two occasions.
Step 2: Detailed assessment of the information to date. Depending on the results, an admission may need to be planned. This will be similar to the severe asthma protocol, and if it is thought that admission is needed, this will be planned in detail.
Step 3 (Nutritional): 3 day admission (see above). Nicola Bridges or Saji Alexander to see with sugar results in OP, GI referral after the admission if we are still struggling. See section 7.1 for algorithm.
Step 3 (Respiratory): Admission for inspiratory and expiratory CT scan, LCI if available, bronchoscopy and pH study. Formal lung function with bronchodilator reversibility, exercise testing, overnight SpO_2 and $TcCO_2$.
(If appropriate, the respiratory and gastrointestinal steps can be combined in one admission)
Step 4: Review of all the above with full MDT, then see consultant, again outside routine clinic, formulation of action plan with the child and family.

6.14 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.**
    - We may try to obtain an induced sputum before deciding on a bronchoscopy (section 6.15e). Arrange with the physiotherapy dept.

2. Therapeutic suctioning:
    - Persistent focal area of collapse / consolidation on chest x-ray, may also include instillation of DNase (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 5.9.

4. Other indications:
    - Intractable wheezing to exclude bronchomalacia.
    - Lavage for fat-laden macrophages to exclude aspiration.
    - Persistent defect on isotope ventilation scan.
    - Lung function lower or LCI higher 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 (ext 2118). 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 but will be in overnight anyway for their pH study.

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 DNase 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 (or worst looking lobe). We always lavage from more than one lobe to increase the microbiological yield.

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

6.15 Chest physiotherapy

6.15a Airway Clearance Techniques

A paediatric physiotherapist is available in clinic to assess all patients and discuss and 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 (this is NOT tipping) and intermittent chest clapping; as well as infant positive expiratory pressure (PEP), assisted autogenic drainage (AAD) and age appropriate exercise.
- **3-4 years and upwards** – Begin with blowing games with the aim to progress to Active Cycle of Breathing Technique in modified or gravity assisted positions. Positive Expiratory Pressure (PEP) and other oscillating PEP devices may be introduced as indicated.
- **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 throughout the patient's life is highlighted in clinic, on the ward and at home visits. Evidence links exercise capacity to improved survival, and therefore exercise forms a key part of treatment and should be carried out alongside ACT. Exercise has also been shown to reduce sputum viscosity, improve ventilation and peak expiratory flow, and facilitate movement of mucus from peripheral to central airways to be expectorated. Current thinking is that exercise should happen between 3 to 5 times per week, lasting for a minimum of 30 minutes per session. Exercise needs to be done consistently, varied, easily fit into the patient's lifestyle, social, give positive feedback and have realistic goals. The aim is to exercise to a target heart rate of 65% of maximal heart rate for the child's age. Consider using technology such as pedometers linked to computer games and web-based exercise logs. At the time of writing the European CF Society exercise working party is producing a clinical practice guideline.

The frequency and duration of ACT 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.
- **Blowing games** including Bubble PEP – ideas include blow football, blow painting, bubbles and whistles. Bubble PEP requires the child to blow into a volume of water (10cms) via a 40cm tube (with washing up liquid) to create bubbles. The water provides

resistance to expiration and therefore creates positive expiratory pressure and oscillation in the airways to mobilise secretions.

- **Positive Expiratory Pressure** (PEP) – Provides resistance to expiration through a mouthpiece or facemask, which temporarily increases functional residual capacity, encouraging collateral ventilation and alveolar interdependence, to recruit closed airways and get air behind secretions. This is followed by forced expirations.
- **Infant PEP** – PEP adapted for infants via a mask over the child's nose and mouth. Performed in the caregiver's arms or seated on their lap, bouncing on a gym ball.
- **High Pressure PEP** – 8-10 regular PEP breaths followed by forced expiration into the PEP mask. This creates pressures of 40-100 cmH_2O and will therefore not be appropriate for all patients. Ask the physiotherapist for advice.
- **Oscillating PEP devices (e.g. Flutter® and Acapella®**). Create positive expiratory pressure and oscillation on exhalation to prevent premature airway closure, mobilise secretions, improve airway patency and reduce sputum viscosity.
  - **Flutter®**– Pipe-shaped device that creates oscillation and positive pressure on expiration used in conjunction with forced expirations**.**
  - **Acapella Choice®** - Uses counter weighted plug and magnet which creates oscillation and positive pressure on expiration. Used in conjunction with forced expirations.
- **Autogenic Drainage (AD) –** Uses controlled breathing which aims to attain the highest expiratory airflows to move secretions from peripheral to central airways while avoiding coughing and significant airway closure/or compression. Breathing is usually from low to high lung volume where secretions are expectorated.
- **Assisted Autogenic Drainage (AAD) -** Used for infants or non-cooperative patients. Manual pressure applied over the chest on inspiration which stimulates the patient to exhale slightly more with each breath and guides the patient towards the desired lung volume to mobilise secretions.
- **Positive Pressure (IPPB or NIPPV)** – Devices using positive pressure to augment tidal volume and reduce work of breathing. Useful in certain situations in hospital and occasionally home. Not to be commenced without discussion from team due to precautions and contraindications associated with positive pressure.
- **HFCWO (Vest)** – Many people ask about the Vest as an alternative treatment technique. Evidence shows that the Vest is less effective in amount of sputum cleared than other airway clearance techniques if used alone. In a long term study over 1 year comparing HFCWO to PEP mask therapy, PEP was associated with shorter treatment times and significantly fewer pulmonary exacerbations and antibiotic use than HFCWO. We will therefore only use the Vest in exceptional circumstances and always in combination with another airway clearance technique.

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

Other physiotherapy issues that may be discussed are:

- **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. The patient can be taught pelvic floor exercises and a technique known as 'the knack' (a pelvic floor contraction). Please consult the physiotherapist for advice.
- Upper Airway Clearance via nasal douching may also be taught where appropriate.

Inhaled medication should be co-ordinated with physiotherapy:

- Bronchodilators - pre-physiotherapy if necessary and benefit shown. No need to do this routinely 10-15 mins before physiotherapy, effect can be quite fast so quicker for child if use it at time of physiotherapy session.
- Hypertonic Saline - Immediately pre-physiotherapy but post bronchodilator. Can also be given during airway clearance if combined with PEP or oscillating PEP. This can save the patient time, but although it improves peripheral deposition, the total lung deposition is reduced, and therefore it is often suggested that the dose should be increased e.g. to 5-6 mls (but not usually done in practice).
- DNase – Timing is decided on an individual basis. In most cases it is given at least 1 hour pre-physiotherapy. N.B some children take it 1-2 hours pre-physiotherapy and a few even longer, occasionally we recommend it is taken before bed but this is a *consultant decision* and coughing overnight should be carefully monitored.
- Steroid Inhalers – Usually taken post physiotherapy treatment. NB rinse mouth after taking a steroid or combination inhaler.
- Inhaled antibiotics - Post-physiotherapy. Either dry powder inhalers or nebulised. Appropriate nebuliser systems should be used.

6.15b Inhaled antibiotic bronchoconstrictor challenge (Drug Response Assessment)

For inhaled antibiotics and hypertonic saline the child must always have a drug response assessment to detect any bronchoconstriction when the 1st dose is given. This should be done in hospital and requires the patient to perform pre and post dose spirometry. If the patient already takes an inhaled bronchodilator then this should be taken before the baseline lung function. The following equation is useful to work out % constricted:

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

- After inhalation of the drug, if the FEV_1 is <15% constricted with no significant adverse symptoms then this is considered a PASS.
- If the FEV_1 is > 15% constricted then spirometry should be repeated after 20 minutes and recalculated.
    - If after 20 minutes, the FEV_1 is still > 15% constricted then this is a FAIL.
    - If FEV_1 is between 10-15% constricted and the patient is symptomatic e.g. audible wheeze, uncontrolled coughing, then it is likely this is unsuitable for use and a FAIL, but this should be discussed with a senior clinician for clarification.

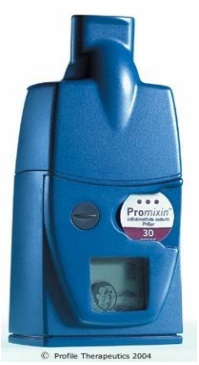
If the patient fails the challenge, we will repeat it at a later date giving an inhaled short-acting bronchodilator before the inhaled antibiotic.

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.
As well as assessing for bronchoconstriction it is also important to ensure the drug is well tolerated and the patient does not have any adverse reactions to it.

6.15c Nebulisers

Nebuliser systems available include Pari LC Plus, Pari eFlow Rapid® and I-neb®. The Pari eFlow Rapid® can be purchased privately, while the I-neb® can be obtained if promixin® is prescribed. These devices may not be suitable for all patients so it is important to get advice from the physiotherapist. If nebulised antibiotics are required in a child under 5 years of age then we recommend wherever possible using a faster nebuliser device (such as the Pari eFlow Rapid). Nebulisers in this age group should be introduced carefully and a staged approach may be useful to reduce anxiety and ensure they are well tolerated in the long run (see appendix VIII).

PHILIPS RESPIRONICS I-neb®



This is a breath actuated device and only emits aerosol on inspiration. It is known as an Adaptive aerosol delivery device (AAD). The breathing modes include tidal breathing mode and target inhalation mode. 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.

Once Promixin has been dispensed (the box of Promixin will contain a disc to make the I-neb work) the patient should contact Philips Respironics directly (08707703434) and a member of their team will arrange to visit the patient at home. They will personally deliver the device, coach the patient how to best use it for efficient nebulisation delivery, and provide details of cleaning instructions and the online download application. This enables the patient to download their I-neb regularly to view treatment times. It also alerts the company to when replacement parts may be required.

PROS	CONS
• Fast nebulisation: Promixin ® (colistin) and DNase 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	• Can only be used if can inhale through mouthpiece (>2 years) • Only available if on Promixin® • Promixin ® more expensive than colomycin ® - £1087 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

• **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 • Face to face training provided by company to optimize breathing pattern and reduce treatment time.	treatment time • Can only nebulise Promixin®, DNase, 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®) • Published data not available that proves Bramitob can be used 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.

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

Grey latched chamber - Promixin®, bronchodilators (1ml fill volume)
Green latched chamber - DNase (1ml fill volume)
Lilac latched chamber - Tobi® (2.5 ml fill volume) and hypertonic saline (2ml fill volume). As the chamber takes a max of 2.5 mls, the dose has to be repeated to give the standard 5 mls TOBI and 4 mls HS.

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 DNase 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)	• £593 + VAT plus at least £120+VAT replacement parts annually (2013 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. Children will also be seen by the Therapy Assistant for regular exercise sessions on and off the ward. 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.

6.15d Dry powder inhaled antibiotics (see also section 6.2a part 6.IIIi).

TOBI® Podhaler

This is licensed in children 6 years and over with an FEV_1 of >25%. When trialling the drug for the first time (even if already on nebulised TOBI®) the patient must be assessed for bronchoconstriction to ensure it is well tolerated. They should be given an appointment for a Drug Response Assessment (see section 6.15b), and to learn how to use the device.

Each dose of Tobramycin inhalation powder is made up of 4 capsules. These are stored in blister packs clearly marked for morning and evening use. Doses are ideally taken 12 hours apart, but definitely not closer than 6 hours apart. As with most inhaled antibiotics it is recommended they are taken after chest physiotherapy. The blister packs are split up into weekly boxes (4 boxes for a 28 day supply), and each box comes with its own Podhaler and storage device. There is also a spare Podhaler and storage device.

Patient information and instruction for use can be found at:
http://www.pharma.us.novartis.com/product/pi/pdf/tobipodhaler_ppi.pdf

It is important that the patient is taught the correct way to take the Podhaler. Ideally a 5 sec inspiration, with a flow of 30 l/min and 5 sec breath hold. We have found an in-check device (in-check™ m – Clement Clark International) useful to guide the patient in performing the optimum inhalation flow of 30 l/min. The child is instructed to perform at least 2 separate inhalations per capsule and following this, it is important to inspect the used capsule to ensure it is empty. If it isn't, it should be replaced in the device (pierced side first) and another inhalation performed.

Common side effects include cough (which in most cases tends to improve on the 2nd cycle of TOBI® Podhaler), sore throat, and changes to voice, fever, shortness of breath headache and haemoptysis.

Colobreathe® Turbospin.

Colobreathe® is licensed in children 6 years and over and administered via a turbospin dry powder inhaler. The first dose should be trialled in hospital to assess for tolerability, bronchoconstriction (see section 6.15b), and for the patient to learn how to use the device.

Colobreathe® 1,662,500 IU inhalation powder is approximately equal to 125mg of colistimethate sodium. The dose for adults and children over 6 years is one capsule inhaled twice daily, ideally 12 hours apart and following chest physiotherapy. The hard capsules are stored in blister packs containing 14 capsules per strip (1 week supply). Each pack contains 4 strips of 14 capsules and 1 turbospin powder inhaler device (28 day supply). Store the capsules at room temperature and not above 25°C. It is recommended that when inserting the capsules into the device, the larger end goes in first, as there have been reports of the capsule breaking thus delivering all the powder in one go; also press the plunger slowly.

It is important that the patient is taught the correct way to take the inhaler. Ideally a 5 sec inspiration, with a flow of 30-40 l/min and 10 sec breath hold. The child is instructed to perform 2-3 separate inhalations for the one capsule, and following this it is important to inspect the used capsule to ensure it is empty. If it is not, it should be replaced in the device and another inhalation performed. Wash mouth out after use to minimise risk of developing oral fungal infection.

Cough and bronchospasm may occur on inhalation but theses reactions usually diminish with continued use. It is recommended to take a bronchodilator prior to its use. Most commonly reported adverse reactions include unpleasant taste, cough, throat irritation, dyspnoea, dysphonia and altered taste. Skin rash may indicate hypersensitivity and therefore treatment should be withdrawn. Less common adverse reactions include headache, haemoptysis, bronchospasm, nausea, vomiting, fever and reduced FEV.

6.15e Induced sputum

Isolation of bacteria from the lower airways is difficult in children who do not cough up sputum. Therefore sputum induction may be recommended for those who have declining lung function and are non-productive of sputum, with no significant bacterial growth. We also consider it for children who have previously grown bacteria only on bronchoscopy and may be at the end of an antibiotic eradication period. We may try to get an induced sputum sample prior to resorting to a bronchoscopy.
An appointment for sputum induction takes approximately 1 hour. It involves the child inhaling 7% hypertonic saline for 15 minutes via an ultrasonic nebuliser device. A cough swab is taken and a bronchodilator is administered prior to the test. In children over 5 years of age spirometry is performed to establish post-bronchodilator lung function. Spirometry is repeated at 5 minute intervals during the nebulisation to assess for bronchoconstriction. At these 5 minute intervals the child will be asked to huff and cough or will be guided to carry out airway clearance techniques to expectorate secretions.

The test can also be performed in younger children who cannot carry out spirometry; in this case oxygen saturations and auscultation is used to assess for tolerability. In children who cannot expectorate, a suction catheter, connected to a sputum trap, can be placed orally to suction secretions.

6.16 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 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 B) needs to be faxed to the relevant oxygen company, depending on the child's GP's address: Air Liquide (London, North West, East Midlands, South West); Air products (York & Humber, West Midlands, Wales); BOC (East of England, North East); Dolby Visiol (South East Coast, South Central, Scotland).

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

6.17 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.

In certain circumstances, where appropriate, an NIPPV device (iSleep) can be loaned for home use so that positive pressure supported airway clearance can be continued after discharge.

7. Gastrointestinal & nutritional care

7.1 Nutritional care & assessment

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.

- Fat-soluble vitamins (A, D, & E) are needed for those with pancreatic insufficiency; vitamin K is given to those aged 6 years or older.

- **Additionally, because of the effects on bone metabolism, we are now also giving vitamin D to children who are pancreatic sufficient, and also vitamin K when they are 6 years old.**

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, chronic underlying infection, 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/cheese/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 encourage more nutrient rich, yet still high calorie snacks.

A specialist dietitian is available in CF clinic and reviews all children on a regular basis. Each review will assess growth, calorie intake, enzyme dosage, and provide education as needed. All children must be weighed and measured at every clinic visit. **Children aged 5 years or less will be measured in their underwear, but those over 5 years can be measured in light clothing and do not need to undress completely.** 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.

Nutritional Assessment

Although nutritional screening of CF patients is similar throughout the UK, there is no recent consensus of how best to assess or identify faltering growth or nutritional failure in children with CF. Previously % weight/height has been widely used, however in our practice we aim to identify children who fall into the following categories:

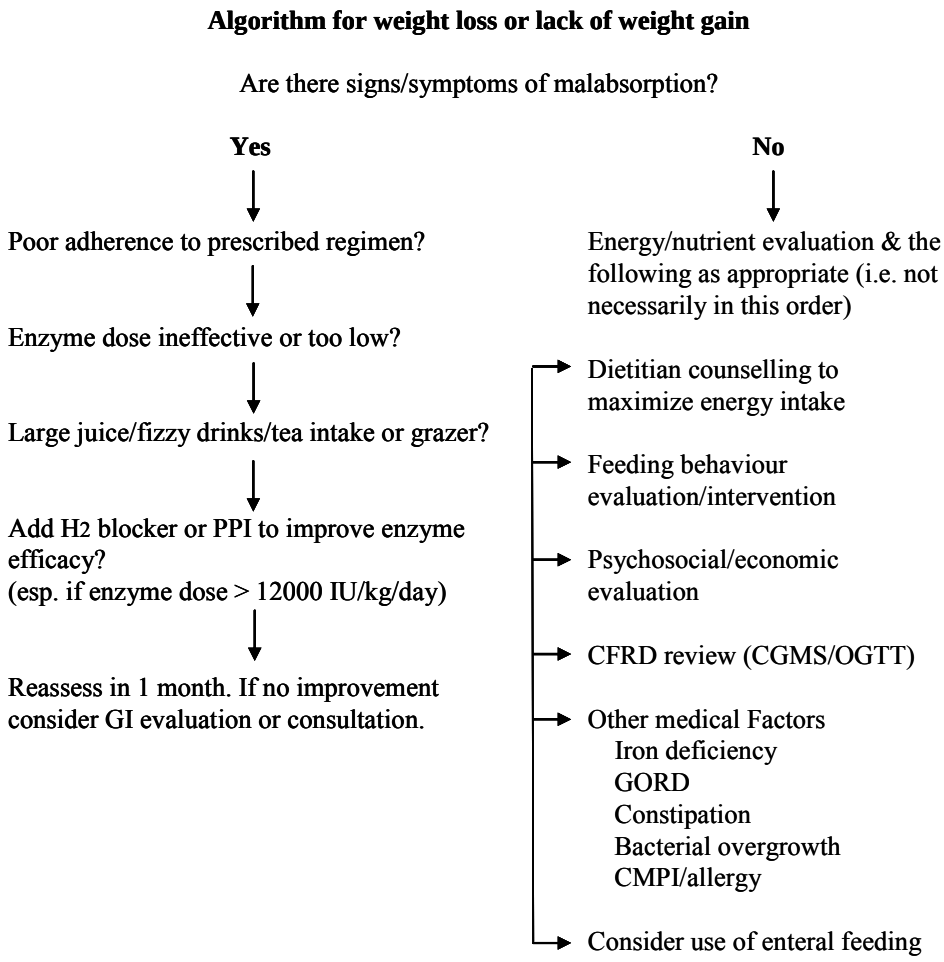
- Infants who have had difficultly regaining their birth weight, who are drifting across centiles in the early stages, and those who suffer with ongoing gastrointestinal issues.
- All children with a BMI of <25th centile.
- Children that cross centile lines in a downward trend. This can be an acute picture or a longer, and potentially less noticeable, change.

Clinical assessment of both height and weight centiles are done using UK WHO Growth Charts. This is monitored closely on a 1-2 monthly basis for infants and 2-3 monthly for older children and adolescents.

Nowadays malnutrition rarely presents as poor height gain alone, therefore if children are identified with faltering growth on their height centiles, they are referred to our endocrinologist Nicola Bridges for further investigation.

Children with unexplained faltering growth should have the following considered –

- Checks for malabsorption e.g. stool microscopy for fat (which may need to be repeated on more than one day); creon intake. Faecal elastase must be measured if the child is previously labelled as pancreatic sufficient.
- Check of calorie intake, with food diary.
- Serum vitamins A, D & E.
- Urinary & serum electrolytes. A spot urine sodium of <20 mmol/L indicates a low total body sodium, and requires correcting in order for weight gain to occur. We do not measure this routinely in newborn screened infants though, unless there is a weight issue.
- CF-related diabetes must be considered.
- Gastrointestinal causes such as lactose intolerance, coeliac disease, inflammatory bowel disease, giardiasis, or short gut syndrome (in those with previous ileal surgery) must be excluded.
- Cow's milk allergy should also be considered in infants.



Adapted from Borowitz et al J Pediatrtr Gastroenterol Nutrition (2002)

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 (usually >500)
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.

If a newborn screened baby is found to be pancreatic sufficient, the stool elastase should be repeated at 3 month of age then at 1st annual review. This may be repeated sooner if results in the less abnormal range (100-250) or symptomatic. After one year, further repeats will only be done when necessary, rather than routinely.

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. Three-day faecal fat collection is no longer carried out, but we will check stool microscopy for fat globules at times (sometimes repeated on more than one day).

There are several enzymes available on prescription but the most commonly used brand is called Creon. Creon contains three digestive enzymes - lipase, protease and amylase. These help digest the different component of foods, fat, protein and carbohydrates respectively. The enzymes come in various strengths including enteric-coated microspheres (Creon Micro), and capsule forms of 10,000, 25,000 units.

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.
- 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 and are generally taken at the start of a meal. However enzymes can be taken at the beginning, during, or at the end of a meal and although there is a lot of research into optimal timing of PERT none is conclusive. The enzymes are most effective for 20-30 minutes so ideally meals should be finished within this time; 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 fruit puree or yoghurt but this may compromise their effectiveness, and can be less convenient, especially as a child get older. Psychology referral may be useful for help with learning to swallow Creon capsules whole, in older children.

Enteric-coated microspheres should be used even in young babies (Creon Micro, Abbott). 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 6 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 causing denaturing of the enzymes in the acidic environment of the stomach. 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 (when available).

There are no specific guidelines for enzyme dosing and the starting doses tend to be as described below. Doses are increased on an individual basis until symptoms of malabsorption are resolved.

- Babies: ½ -1 scoop of Creon micro granules per breast feed or equivalent formula feed (of 120ml). 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 only occasionally prescribed to older children and adolescents.

As a general rule doses exceeding 10,000 IU lipase/kg are avoided, however it is frequently observed that many children require doses higher than this to control symptoms of malabsorption, especially during stages of accelerated growth. When a child is on a particularly high dose, the Creon prescription and other routine clinical investigations would be reviewed in full to ensure there is not an additional underlying reason for malabsorption.

Excessive doses can cause perianal irritation and barrier nappy cream is useful in babies with a sore perianal area to prevent excoriation. In very high doses, hyperuricaemia and hyperuricosuria can occur, although this is rare. 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.

7.3 Oral nutritional support

There is a wide range of prescribable products available – largely drinks and fortifiers - for children who are identified as having faltering growth. Following appropriate dietetic counselling children may be commenced on supplements.

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 at different times to mealtimes, or at bedtime. Parents can use supplements creatively (e.g. in cooking) to encourage intake and avoid taste fatigue. In our experience, good compliance and short term use of supplements maximises their effectiveness. 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 (SMA) • Infatrini (Nutricia) • Similac High Energy (Abbott) • Concentrated Standard infant formula – *must* be supervised by the dietitian
	Paediatric	• Paediasure Plus (Abbott) • Fortini & Fortini smoothies (Nutricia) • Frebini Energy (Fresenius Kabi)
	Adult (1.5-2.6 kcal/ml)	• Build-up (Nestle) • Ensure Plus (Abbott) - Also available in yoghurt style flavour • Ensure TwoCal (Abbott) • 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)	• Ensure Plus Juice (Abbott) * • Fortijuice (Nutricia) * • Provide Xtra (Fresenius) * • Clinutren Fruit (Nestle) *
Powder and liquid polymers to add to foods	<u>Carbohydrate:</u>	• Maxijul (SHS) * • Polycal (Nutricia) * • Polycose (Abbott) * • Caloreen (Nestle) *
	<u>Fat emulsions:</u>	• Calogen (Nutricia) • Liquigen – MCT fat (Nutricia) * • Fresubin 5kcal shot (Fresenius)
	<u>Carbohydrate + fat mixtures:</u>	• Duocal (Nutricia) * • Procal and Procal ‘Shot’ (Vitaflo)

** DO NOT NEED ENZYMES*

- Many specialist infant feeds will still require enzymes, for example: Neocate LCP (Nutricia), Nutramigen (Mead Johnson), Aptamil Pepti (Aptamil).
- The following feeds are also likely to still need enzymes but in smaller doses; Pregestimil (Mead Johnson) and Pepti-Junior (Cow and Gate).

7.4 Enteral nutritional support

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:

- Intensive dietetic support with 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
- Exclusion of other conditions, especially CFRD and Pseudo-Bartter's syndrome.

The following investigations should be carried out, and this may be done as part of the challenging CF protocol (section 6.13):

- 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, likely secondary to increased awareness of the importance of nutrition at an early age, and the implementation of the new born screening programme.

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 a night off each week can help with compliance, especially in teenagers.. 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.

Concomitant gastro-oesophageal reflux must be considered, possibly with a pH study; as a Nissen’s fundoplication may be necessary as a gastrostomy can worsen reflux.

The procedure is either carried out at the Royal Brompton or at Chelsea & Westminster Hospital. This is by a Consultant Paediatric Gastroenterologists, usually Dr John Fell, together with Mr Muntha Haddad or Mr Simon Clarke (Consultant Paediatric Surgeons).

To **organise** a gastrostomy, please contact the Gastroenterology Dept. secretary on 0208-746 8000 ex 58628 or 58885. 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. The child is

admitted for the peri-operative antibiotic regimen (see section 10.1). 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. After placement, feed initiation and post-gastrostomy care should be followed according to the advice from the surgeon, or as per the Royal Brompton Hospital 'Policy for the use of gastrostomy devices (adult and paediatric)' which is available on the intranet.

For problem solving with gastrostomies first refer to the link nurse on Rose Ward. For any further complications contact the Paediatric Gastroenterology Nurse at Chelsea & Westminster Hospital on 0208 746 8627 or 0208 746 8000 Bleep 4988.

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 polymeric 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.

Although not licensed, in practice Creon Micro is sometimes put down a feeding tube. This 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 powder formulations can be used.

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) fat source may be considered. Because of the nature of these feeds some 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 Adult feeds (>20kg)	Tentrini Energy	✓			1.5 kcal/ml (7-12 years / 21-45 kg)
	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 funded from the local GP and CCGs and the dietitian will make arrangements for these to be supplied at home.

7.5 Management of feeding difficulties

Feeding difficulties are not uncommon in patients with CF which can be challenging for their physical health, and for their families and professional carers to manage. It is really helpful for CF children and their parents to develop a relaxed and positive attitude to food and nutrition despite the strong emphasis from us the RBH CF team on weight and growth.

Feeding difficulties can consist of a combination of unhelpful but ordinary child behaviours (e.g. food refusal, fussy eaters) and parental responses which can reinforce this (e.g. shouting or making multiple meals if the family meal is refused).

Most children will go through phases of feeling less or more inclined to eat 'well'. Parents who are concerned about their child's feeding behaviour or who would like some suggestions to minimise stress at mealtimes are very much encouraged to contact the dietician, clinical nurse specialist and /or clinical psychologist directly, or ask to be referred by another member of the team. The sooner this happens, the better for the whole family.

For most parents weaning infants onto solid food is an enjoyable experience; however they can often 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 principals 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 - which includes offering a reasonable portion in the first instance (too large and the child might just give up, they can always ask for more).
- 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 up to 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.

7.6 DIOS and constipation

Distal Intestinal Obstructive Syndrome (DIOS) is a common complication in CF (paediatric lifetime prevalence of ~8%). The incidence varies widely but it mostly affects those with pancreatic insufficiency. The pathophysiology is not fully understood, but there are often multiple contributory factors including:

- Severe genotype
- Pancreatic insufficiency
- Inadequate salt intake
- Dehydration
- Poorly controlled fat malabsorption
- History of meconium ileus or DIOS
- Post organ transplantation

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. Children often report having their bowels open as usual, or sometimes diarrhoea (from overflow).

Important features that increase suspicion of DIOS are:

- Acute periumbilical or right lower quadrant abdominal pain
- Vomiting
- Palpable mass in right lower quadrant

Differential diagnosis

Constipation (commonest), adhesions post abdominal surgery, appendicitis, intussusception, volvulus, 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. Intestinal fluid levels and iliocaecal mass suggest DIOS.

If there if are doubts over the cause of abdominal pain, the following may be helpful:

- WBC, amylase, liver function tests.
- Urinalysis
- Abdominal ultrasound.
- Barium /gastrografin enema - by specialist radiologist can diagnose and help treatment at same time.
- After the acute episode, consider microscopy for fat globules.

Management of DIOS

1. Acute

- ***Rehydration*** - patient must be **well hydrated** before, during and 3 hours post treatment, as gastrografin is highly osmotic. This is often done as an in-patient, especially in the more severe cases IV fluids may be required. The suggested fluids below are the minimum. Be particularly careful in babies & infants who can easily become dehydrated.

- ***Gastrografin*** (oral) – see also formulary 11.2e.

  25 mls (<15kg) with 75 ml water or juice
  50 mls (15-25kg) with 150 ml water or juice
  100 mls (>25kg) with 200 ml water or juice

  - 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- same dose as oral, diluted as per formulary 11.2e. 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.

Other treatments -

- 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

- Polyethylene glycol (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).

- Colonoscopy or surgery is rarely required although is indicated where above medical management has failed. May involve laparotomy and enterostomy or even bowel resection.

2. Chronic (management post acute event)

Laxatives e.g. Movicol or Lactulose should be continued for 6-12 months post DIOS. See Formulary 11.2f.

- Avoid dehydration - ensure adequate fluid & salt intake.
- Check dose / compliance / timing of enzyme supplements.
- If ongoing malabsorption is documented consider starting ranitidine or omeprazole .
- Diet – ensure adequate dietary roughage.
- 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 continuing problems refer to Dr John Fell or one of the other GI consultants at Chelsea and Westminster Hospital.

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 or Movicol may be used (see formulary 11.2f). Lactulose can cause stomach cramps and flatulence in large doses.

7.7 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. It will be repeated in 1 year if abnormal.
- 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, and azithromycin (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. Octreotide can be started on Rose ward prior to transfer but does have implications for nursing care.
    - **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.

7.8 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). If ferritin is high, check what the CRP was to see if it is likely to be an inflammatory response.

We are now only measuring Hb, MCV and ferritin to assess iron status at annual review.

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
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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 distinct from either type 1 or type II diabetes mellitus and we have different approaches to diagnosis and management.

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.

WHO criteria for diabetes and prediabetes (2006 and 2011).

Diabetes- any of these

- Fasting glucose ≥7.0 mmol/L
- Two-hour post glucose challenge value ≥11.1 mmol/L.
- HbA1C value of ≥6.5% (48 mmol/mol) can be used as a diagnostic test for diabetes. (A value of <6.5% does not exclude diabetes).

Impaired glucose tolerance (IGT)

- Fasting glucose <7.0 mmol/L **and** a two-hour glucose post glucose challenge of ≥7.8 mmol/L but <11.05 mmol/L

Impaired fasting glucose (IFG)

- Fasting glucose of 6.1 - 6.9 mmol/L.

Why we treat CF related diabetes and impaired glucose tolerance

CFRD reduces life expectancy and there is evidence that management of diabetes improves outcome, so CFRD has become an important aspect of CF management. 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. Insulin treatment has been demonstrated to improve these clinical markers. Diabetes in CF is caused by insulin deficiency, so insulin is the logical choice for treatment. Oral hypoglycaemic agents have not been shown to give the same benefits to clinical status as insulin. The risk of microvascular complications in diabetes is related to control (measured by HbA1c) and the duration of diabetes, and appears to be the same in CF as in other forms of diabetes.

The adverse impact of insulin deficiency is associated with loss of the anabolic effect of insulin, loss of nutrition related to glycosuria and possibly increased infection risk with elevated glucose.

The diagnostic categories for diabetes and prediabetes based on oral glucose tolerance tests or fasting glucose (see above) are based on the risk factors for cardiovascular disease in type 2 diabetes. In CFRD there is evidence of clinical impact from glucose abnormalities which do not meet the criteria for a diagnosis of diabetes, and also evidence of benefit from treatment of impaired glucose tolerance. Most clinicians use these standard definitions for diabetes in CF but because the clinical situation is different treatment may be given to individuals who do not meet the criteria for diabetes.

Screening for abnormal glucose tolerance and diabetes in CF

When to test for glucose status in CF:

- Current CF Trust recommendation is for OGTT once yearly in all CF patients over 12 years. **Our new policy is to carry out CGMS in 12 & 15 year olds around the time of their annual reviews, rather than annual OGTT.**
- 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, whatever they eat). Formal assessment is required if there are repeated glucose levels >8.0 mmol/l or a single level >11.0 mmol/l.
- HbAic on annual review or at other times **>6.5%** (IFCC HbAic **>48** mmol/mol).
- 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)
- Oral glucose tolerance test
- Random glucose tests
- HbA1c

CGMS

How it works - A subcutaneous sensor gives a profile of glucose levels for up to 6 days. A plastic sensor reads glucose in the interstitial fluid every 2-3 minutes. The sensor needs to be

calibrated with blood glucose measurements **twice daily** for as long as sensor 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. CGMS gives a very comprehensive picture of glucose status over a number of days and is the best way of deciding on whether to treat with insulin.

When to use CGMS

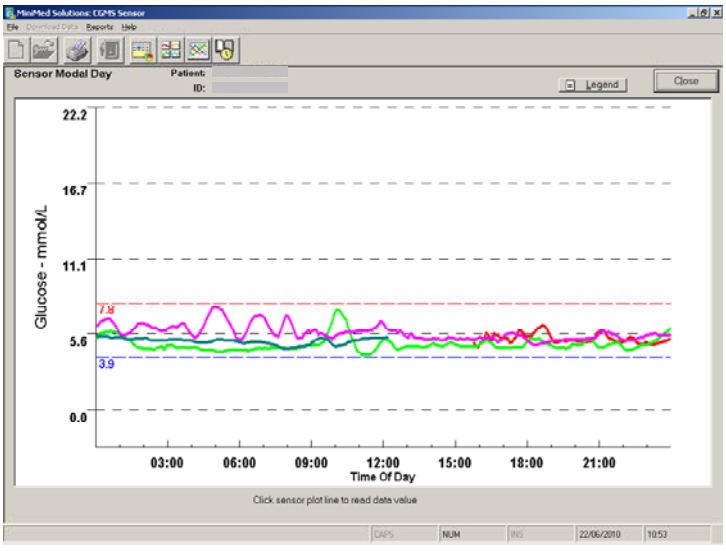
- To decide on the need for treatment if there are high random glucose measurements (>7.8 mmol/l).
- If there are clinical concerns (poor weight gain, decline in lung function) and other possible causes have been addressed.
- To guide choice of insulin regimen (see below).
- To give information on control for individuals already on insulin (for example whether overnight feeds are adequately covered by insulin).
- 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.

Advantages

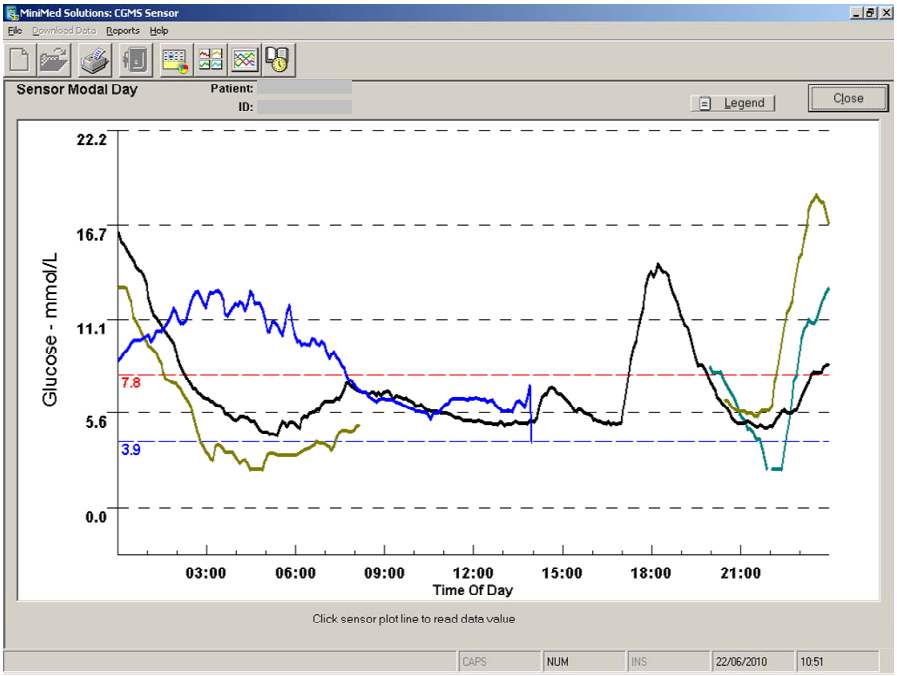
- CGMS gives a better picture of glucose status in CF than either OGTT or random glucoses and can demonstrate glucose abnormalities that would not otherwise be detected.
- The effect of food, exercise and treatment on glucose levels can be assessed.
- It may be a better guide than OGTT as to when to 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).



Abnormal CGMS trace



Oral glucose tolerance test

How it works - Glucose levels are measured before and after a standard oral glucose load.

- *Preparation*
  The child is fasted from midnight although drinks of plain water are allowed.

- *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 60 + 120 minutes.
  - A sample at 30, 60, 90 and 150 minutes will add further diagnostic information, take these samples if there is a cannula in place. These measurements are not required for the diagnosis of diabetes.

  The diagnostic guidelines are based on venous blood samples and not fingerprick samples. The accuracy of bedside blood glucose meters is good but only do this if you are forced to because of needle phobia.

- *Non fasted glucose challenge*

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. The results of a non

fasted OGTT do not define glucose tolerance status in the same way as a standard OGTT, but abnormal glucose levels found during testing are still significant.

When to use an OGTT

- As a quick 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.

Advantages of OGTT -

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

Disadvantages

- In CF because individuals with impaired glucose tolerance get benefit from treatment OGTT is not a clear guide as to when to treat.
- The OGTT will miss a significant number of individuals with abnormal glucose tolerance in CF, particularly if only baseline and 120 minute tests are done.

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. 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. In CF fasting (pre breakfast) glucose levels can be normal even if the glucose levels later in the day are very high.

When to use random glucose profile

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

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.

HbA1c

The value as a screening test in CF is not clear. If the HbA1c is over 6.5% (48mmol/mol) glucose levels are not likely to be normal and CGMS or OGTT is indicated.

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. Oral hypoglycaemic agents can control glucose levels in some individuals but there is no sustained benefit to clinical state, **so we do not use them.**

Who should be treated?

- Everyone with a diagnosis of diabetes as defined above or with an elevated HbA1C 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

Discuss treatment with one of the paediatric diabetes team - 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. You may need to use Novorapid to cover meals as well.

- 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. Start at a low dose and gradually increase.
- 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.
- For overnight feeds adjust on the basis of glucose levels in the middle of the feed and as it finishes.
- 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. Do not treat as hypoglycaemia unless glucose levels <4 mmol/l.

- 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.
- Spontaneous hypoglycaemias (from endogenous insulin production) are also seen in CFRD and glucose intolerance.

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 4 mm 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. CFRD gives the same risks of microvascular complications as any other type of diabetes and adults with CFRD should be regularly screened.

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.
- Encourage good habits- blood testing at appropriate times, eating snacks and meals on time and not omitting insulin.
- Make sure you have the right equipment- the right strips for the meter, the right pen for the cartridges.

Prescribing insulin

Safe use of insulin
All health care professionals prescribing or administering insulin should have had training in safe use of insulin. There are many clinical incidents in the UK each year related to insulin prescription and administration. Common incidents include giving the wrong insulin, lack of clarity in prescriptions, and drawing up or giving insulin with the wrong type of syringe.
Safe insulin prescriptions
- Get the correct insulin name (there are some insulins with similar names) but also the presentation, e.g. cartridges, disposable pen.
- State when the insulin is to be given. For short acting insulin this will be before a meal and not at a particular time of day.

- If the dose is variable (for example short acting insulin for meals) you must make it clear how the dose will be decided.
- For paper prescriptions the word "units" must be written in full and never "u" or "iu". This is a cause of drug errors because a badly written "u" can be taken to be a zero.

Safe insulin administration

- Even if the patient has been having insulin treatment for a long time it is important to check the dose, administration technique and the injection sites.
- The person signing for the insulin dose takes responsibility that the correct dose is given. **Even if the parent or patient is giving the insulin, check the dose and the correct administration.**
- Always use an insulin syringe to draw up insulin for an insulin infusion

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: www.bsped.org.uk/).

Other practical aspects

Schools. The school may need information. A plan needs to be made if blood testing or injections are occurring during school. Legally, schools must provide support for children with medical needs. It is possible for school staff to check glucoses or give insulin if they have training and a clear plan. Even if insulin is not given during school times, blood glucose monitoring must be facilitated at 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

Travel. 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). All equipment and insulin must be in their hand luggage.

Driving. There are strict rules covering driving and diabetes which change from time to time. Some types of licence cannot be obtained if you have diabetes (some classes of HGVs). Currently everyone with diabetes must renew their licence every 3 years. Patients applying for a licence must declare their diabetes and must get medical confirmation that they are well controlled and are testing glucose regularly.

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

Average birth weight and length is slightly reduced in CF compared to unaffected infants. In unscreened infants growth rate (weight and length) is reduced 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. Individuals diagnosed after newborn screening are taller in childhood than unscreened children picked up later on clinical grounds.

Improvement in the treatment of CF over time has resulted in the patterns of growth in childhood moving nearer to that of unaffected children. There still appears to be a small height deficient in childhood related to CF. Height velocity in childhood is within normal limits. The height deficit can increase further in adolescence because of delay in puberty and in some cases, worsening clinical status. 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.

Normal growth
Movement across height and weight centiles (up or down) is common in the first 2 years of life and does not necessarily represent a problem. Our data show nutritional status should be normal by 1 year. Most children will settle onto a height centile by 2-3 years of age and after this a child who is growing normally will maintain a height velocity sufficient to keep on the same centile, and will carry on growing along this centile until they commence their pubertal growth spurt. A child with late puberty will have a fall in height centile position and also feel relatively shorter compared to their peers, until they start their pubertal growth spurt. 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.

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. Mid parental height and parental target centiles should be calculated as shown on the growth chart.

Further assessment is required for children who:

- Are falling from their centile position- they have a poor height velocity over a reasonable period of time (6 months to a year)
- Are very short (below 0.4th centile) even if they are growing at a normal height velocity
- Are very short for their mid-parental height.

- Have significant pubertal delay (see puberty section 8.3)

Assessment

Look for factors related to CF which may impact on growth.
- Nutrition - intake or malabsorption. Feeding behaviour problems are common in younger children (see section 7.5).
- chronic infection
- impaired glucose tolerance or CF related diabetes
- steroid treatment
- 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).

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

Investigations which can be done before referral
- Thyroid function, coeliac antibodies and karyotype in girls.
- Bone age (x-ray of the non-dominant wrist and hand) is a way of looking at how much growth there is still to come. 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.
- One off measurements of GH are not helpful. IGF1 and IGFBP3 are helpful in assessing GH activity but do not distinguish between defects of GH secretion (pituitary problems) and GH action (inflammation, infection, steroids).
- For pubertal delay it may be helpful to check LH, FSH and sex steroid levels although these are likely to be low until mid-puberty.

Consider referral to paediatric endocrinology for the following reasons:
- Pubertal delay (see puberty section 8.3).
- Reduced height velocity or short stature, which does not seem to be caused by CF related problems.
- Concerns by family or child about height.
- Assessment may be of value if there is persistent poor growth velocity even if) there are medical factors sufficient to completely explain the situation (nutritional issues, inflammation, reduced lung function, high dose steroids, etc). There may not be any intervention to improve things but an assessment and explanation may help.

Growth hormone
GH deficiency is a rare cause of short stature in the general population. It can occur in CF but the prevalence is not increased. GH deficiency should be considered in short children with persistent poor growth velocity where other causes have been ruled out. Diagnosis requires a stimulation test.

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. The impact of GH on longer term clinical status is not known, and there is no evidence that GH given in this situation increases adult height. GH is not licenced for use in CF without GH deficiency.

8.3. Puberty

Pubertal delay remains a problem in CF although the improved clinical status of those entering adolescence has made this less common. Delayed pubertal development has been found to contribute significantly to the psychological problems suffered by adolescents with CF. Presentation may be with short stature or with concerns about development.

Gonadotrophin and sex steroid secretion is normal during puberty in CF and adult sex steroid levels are usually within the normal range. Boys reach normal testicular volumes in puberty despite the majority having azoospermia.

Assessment of pubertal delay

- Height & weight.
- Tanner staging. (these are printed on growth charts).
- Bone age if there are concerns about height.
- LH, FSH and sex steroid levels although these are likely to be low until mid-puberty.

In girls:

- The first sign of puberty is breast development (Breast stage 2)
- The pubertal growth spurt starts as puberty commences (Breast stage 2)
- Periods occur relatively late in development, at Breast stage 4 or 5.
- Growth slows after menarche, with about 4-5cms remaining.

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

In boys:

- The first sign of puberty is an increase in testicular volume (4mls and over). This means that the start of pubertal development may be overlooked if testicular volumes are not assessed (and may not be noticed by the individual themselves)
- The pubertal growth spurt in boys does not start until mid-puberty (10-12mls testicular volume).
- The voice breaks towards the end of puberty

  Ask if pubic hair is present
  Has voice broken?

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. If it is unlikely that any significant change will occur (and things might get worse), 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. Many 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.

<u>Steroid treatment for induction of puberty</u>

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

Topical sex steroids to induce puberty
There are very few published data on preparations or doses. There is one published study using "Evoral 25" oestrogen patches, (one eighth or one quarter of a patch every 48 hours) in girls. "Tostran" metered dose topical testosterone is a possible option for boys but there are no supporting publications.

8.4 Bone Metabolism

A CF Trust guideline (2007 with an important addendum) is available and the link is: https://cysticfibrosis.org.uk/media/82016/CD_Bone_Mineralisation_Feb_07.pdf

Bone density in CF
Approximately 25% of adults with CF have osteoporosis and there is an increased risk of vertebral and non vertebral fractures, which is significantly worse in individuals post-transplant. The aim of monitoring and therapy is to reduce the morbidity related to fractures. Bone density increases during puberty under the influence of sex steroids, peaks in early adult life and falls after this, so in children and adolescents with CF it seems logical to try to get the best bone density possible in the hope of reducing problems which may occur many years later.

Investigation of bone mineralisation by DEXA scans
Dual energy X ray absorptiometry (DEXA) is the commonest way of examining bone density in children and adolescents, looking at the spine and upper femur. Bone mineral density (BMD) is calculated from the bone mineral content (BMC) measured by DEXA and the 2 dimensional area of the bone calculated during the scan. The measured BMD of larger bones will be greater without the actual density of the bone being more because the beam will pass through a bone of greater dimensions. This makes assessment of BMD in growing children complex. Bone mineral apparent density (BMAD) is a correction factor aimed at overcoming this problem. There are normal ranges for bone density in healthy children and the measured BMD will be compared with this (z score). Interpretation of the z score may be difficult if the child is very short (and compared with children with larger bones) or delayed in puberty (and compared with children with normally timed puberty). The trend between repeated measurements may be more helpful than comparing with the normal range.

Risk factors for reduced bone mineral density

- **Steroids** Frequent courses of oral or intravenous steroids and those on high dose inhaled corticosteroids.
- **Vitamin D and Calcium** are vital in bone growth**. Everyone** with CF (including pancreatic sufficient) should take vitamin D supplements, (see below for management of deficiency). Encourage intake of diary products and consider supplements in those who do not.
- **Nutritional status-** nutrition apart from calcium and vitamins influences bone growth. CFRD can contribute to reduced bone density.
- **Vitamin K** is a fat soluble vitamin vital for the function of osteocalcin and other bone related proteins, and may 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 for ALL CF children when 6 years old (it can be dissolved in water if necessary). We are also starting ALL newborn

screened babies (including pancreatic sufficient babies) on aquadeks which contains a small amount of vitamin K,

- **Infection**- chronic inflammation can inhibit bone formation.
- **Endocrine issues** - sex steroids are vital in the attainment of adult bone density during puberty and adult levels of sex steroids are required to prevent osteoporosis in adults.
- **Physical activity** -exercise, particularly weight bearing is needed for normal bone growth and children who do not move much will have reduced bone density.
- **CFTR** is expressed in bones and mutations in CF may contribute to reduced bone density.

Screening of bone density
Bone densitometry (DEXA scans of lumbar spine and femur) is measured in all patients from age 8 years every 2 years at annual review. Look at the vertebrae on chest x-rays for any evidence of injury/crush fractures.

Repeat the scan after 12 months if:

- BMD z score is $\leq$ -2.0.
- The child has had fractures which do not seem to be related to sufficient trauma.
- They are in a very high risk group for osteoporosis (high dose steroids, poor nutritional status, long periods of inactivity).

Abnormal scans can be discussed with Dr Nicola Bridges or Dr Saji Alexander (Chelsea and Westminster). They will be repeated in 1 year.

Prevention of osteoporosis- everyone with CF

- Vitamin D supplements and treatment of Vitamin D deficiency
- Monitoring and treatment of pubertal delay
- Assessment of sex steroid levels in adults
- Encouragement of weight bearing exercise

Management of reduced bone density and osteoporosis

Consider the following factors if BMD z score is $\leq$ -2.0. If the BMD is low on repeated DEXA scans or the child has had fractures which do not seem to be related to sufficient trauma, a more formal assessment of bone health or a referral are required.

- *Pubertal delay and hypogonadism* 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.
- *Clinical factors* - CFRD, reduced lung function (FEV_1<50% predicted), nutrition, immobility
- *Vitamin D and calcium* status

Bisphosphonate treatment
Bisphosphonates reduce turnover and result in increased bone density. They can be given intravenously (pamidronate, usually given as a 3 monthly IV infusion) or orally (a number of agents but there are significant cautions about how the tablets should be taken and there are no liquid preparations). Bisphosphonates have been demonstrated to reduce fracture risk in some conditions, but studies specifically in CF have not confirmed this.

In children and adolescents bisphosphonate treatment should be considered if all of these apply:

- after other issues (as above) have been addressed.
- Serial BMD z score is -2.0 or less in total body or lumbar spine.
- there is a history of low trauma fractures in limbs or vertebrae.

Potential side effects of bisphosphonates:

- osteonecrosis of the jaw can occur and those with poor dental hygiene are at most risk
- there is an increased risk of atypical fractures of the femur
- bisphosphonates are teratogenic in animal studies and are contraindicated in pregnancy. In addition because they bind to bone and are then leached out over a long period there is the theoretical risk that a fetus could be exposed if the mother had treatment in some time before pregnancy.

Bisphosphonates are unlicensed for this indication and treatment should be discussed on an individual basis in conjunction with Dr Bridges or Dr Alexander.

Vitamin D status

We measure 25 hydroxy-vitamin D levels 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.

Optimal levels vitamin D	> 75 nmol/L
Vitamin D adequate -	50 -75 nmol/L
Vitamin D insufficient -	25 -50 nmol/L
Vitamin D deficient -	< 25 nmol/L

- We treat all children with vitamin D supplements (colecalciferol) if levels are <50.

- If levels are 50-75, we would increase their daily vitamin A&D (or dalivit) assuming vitamin A levels allow that (i.e. vitamin A is not high). Clearly there is a spectrum so that we might chose to give 3 month treatment dose if levels are in 50s, especially if the DxA scan shows reduced BMD.

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.

10 mcg of colecalciferol is equivalent to 400 units.

All newborn screened babies (pancreatic insufficient and sufficient) are being started on Aquadeks which contains vitamin D.

Treatment of vitamin D deficiency

Any one with a vitamin D level below 50nmol/l should be treated.

Give oral colecalciferol 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 liquid 3000 units/ml. 10 mcg of colecalciferol is equivalent to 400 units.
- *or* colecalciferol 20,000 units capsules given three times a week – Mon, Wed & Fri;
- *or* colecalciferol 50,000 unit capsules given once a week.

Intramuscular calciferol preparation is an alternative -

- Child 6 months-12 years: single dose of IM Calciferol 150,000 units
- Over 12 years: single dose of IM Calciferol 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. In practice, it is difficult to get levels to stay up. Also levels are reduced in winter so consider when the blood was taken.

Do not increase the dose of Vitamin A+D capsules 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.

8.5 ENT complications

8.5a 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.

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

If troublesome:

- Initial treatment is usually a steroid nasal spray such as fluticasone (Flixonase or Avamys) 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 (020 3315 7972). Mr Jonny Harcourt is present in Brompton clinic on the 2nd Friday of every month from 11am-1pm, and can see the children as well; simply book the patient directly into his clinic and send him a letter.

8.5b Sinusitis

- Although almost all children with CF have chronic paranasal sinus retention of secretions and mucosal inflammation, 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. CT scans are the investigation of choice (not MRI) but should only be considered if it a complication (such as a mucocoele) is considered or if the patient is failing conservative treatment and surgery is a possibility.
- Nasal swabs are extremely useful as a wide spectrum of bacteria may be involved.
- Chronic sinus infection, with associated upper airways obstruction, may worsen lower respiratory tract health.
- Chronic sinusitis is commonly associated with nasal polyposis.
- Sinusitis may cause headaches, which are persistent and localised. 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.
- Invasive sinus washout (needle inserted into maxillary antrum) is not recommended, unless to provide a sample for culture, as it has no long term benefit. However a nasal douche may give symptomatic relief.
- In a minority endoscopic sinus surgery is appropriate if severe localised headaches, usually combined with persistent offensive nasal discharge persists despite initial medical treatment with antibiotics and steroids.
- Mucocoeles may occur as a complication of CF in the sinuses. A single air cell becomes blocked, retains its secretions and becomes slowly enlarged. This may be a painless process though maybe complicated by an acute infection. If advanced the condition can cause proptosis or hpertelorism. Surgery is highly effective in draining the chronic infection and preventing further expansion of the paranasal sinuses.

8.6 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 6.12) 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.

8.7 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.

8.8 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.

8.9 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, but initially the are seen by one of our physiotherapists, as sometimes simple 'pelvic floor exercises' and a technique known as 'the knack' (a pelvic floor contraction) can be quite helpful.

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 Martin Carby or Dr Anna Reed, Consultants in Respiratory & Transplant Medicine, at Harefield Hospital.

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.

Traditionally, children fulfilling these criteria would be likely to have a median life expectancy of 2 years, but this may not be the case anymore.

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 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:……..

……
……

……
……

……
……

……
……

……
……

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 usually 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 or Dr Saji Alexander.
- Beware dehydration or opiates 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 Prof 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 dose each year. For some of the needle phobic children, we will carry out the immunisation ourselves in clinic. The injection 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 BNFc). Egg hypersensitivity with evidence of **previous anaphylaxis** is a contraindication. Parents should also receive the vaccine (but we do not routinely give to siblings).

There is now a live attenuated intranasal influenza vaccine available for those aged 2 years and above (Fluenz®). Information is available on www.gov.uk/government/uploads/system/uploads/attachment_data/file/239268/Green_Book_Chapter_19_v5_2_final.pdf. We have no experience, and there is no evidence yet for its use in children with CF, so we are recommending the standard intramuscular vaccine for the winter 2013/2014 until more information is available.

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. In older children (if they did not receive Prevenar) 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 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.

At the 6th birthday annual review, we measure varicella antibodies, and if negative, we will offer **varicella immunisation** (even if there is a history of having had chicken pox). 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 published 2011. http://www.brit-thoracic.org.uk/Portals/0/Guidelines/AirTravelGuidelines/BTS%20Air%20travel%20recommendations%20September%202011.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. DNase 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 in clinic or from the CF secretary (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% 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 (usually free of charge now). 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/living_with_ph/airline_rules_on_oxygen.php

   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

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.

End of life care will be discussed with the parents by the child's consultant. These discussions, where possible and appropriate, should include the child. 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 can include either staying at the tertiary centre, going to a hospital locally, a hospice or home. Informed discussions about the provisions available (including support and expertise) should be openly discussed with the family.

Specialist Paediatric Palliative care services are available to provide symptom management, support advance care planning and end of life care. All services offer a 24-hour telephone advice service for families and professionals:

1. The PATCH (Paediatric Palliative Care) service (based at Royal Marsden)
Contact: 0208 661-3625 (Mon-Fri daytime) and out of house via Switch board (0208 642-6011) and ask for the PATCH service.

2. The GOSH palliative care team
Contact: 020 7829 8678 (Mon- Fri daytime) and out of hours via Switchboard 0207 405 9200 and ask to be put through to the palliative care team

Additionally: The adult Palliative care team (Royal Marsden) provides a specialist adult service at the Brompton. Their service may be more appropriate in the older teenager and young adult population.

End of life care

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.

- An advance care plan including symptom plan, preferred place of care and death, wishes and emergency resuscitation plan should ideally be in place prior to, or at the start of, the end of life phase.

- Clear and open discussions about the appropriateness and need for specific observations, interventions and treatments should be discussed with the family and documented in the medical records for staff. This could include blood sampling and routine basic observations e.g. blood pressure monitoring. Intravenous access is usually unnecessary, since symptoms can often be managed via buccal, transdermal, enteral or subcutaneous routes.

- Regular review by the child's lead Consultant and Specialist nurses should continue and local services and involved professionals should be updated on any changes in the child's condition.

- Some of the medications should be continued, although only those offering symptomatic relief *e.g.* bronchodilators, enzymes supplements, humidified oxygen. Drugs such as antibiotics, vitamins, calorie supplements may offer no ongoing benefit at this stage.

- 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 should be agreed.

- Each child and their family have specific cultural and religious needs, these should be sensitively explored. 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 their family. The child and families local faith leader is welcomed if preferred by the family.

- Support for staff should be offered.

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.

Emergency care and resuscitation plans are replacing DNR forms in many services. They provide a more comprehensive and detailed account of the levels of intervention offered to a child experiencing various clinical scenarios.

Care at home
Should the family have decided to care for their child at home the local Paediatric & community teams will take the lead role in the child's care, with support from specialist palliative care services, and the CF community outreach team. The Specialist palliative care service will help facilitate the transfer of care and support the child and their family in all settings.

Medication for symptom relief

'APPM Formulary' provides up to date guidance on medication for children in the palliative care setting in the UK (it is also used throughout the world). This formulary is available free online and is regularly updated. The formulary is written from best evidence and expert advice - www.**appm**.org.uk/10.html.

'Prescribing in palliative care' in British National Formulary for Children (BNFc) also provides advice around prescribing and drug doses.

1. **Analgesia**
   - Paracetamol - oral / rectal.

   - NSAIDs e.g. Ibuprofen- oral.
     can be given with paracetamol.

   - Short acting (immediate release):
     - Morphine: Oromorph (liquid) or Sevredol (tablet)

- Oxycodone: Oxynorm (liquid or tablet)
- Fentanyl: Fentanyl buccal or sublingual or intranasal spray

Each drug has a different time to onset of action and clearance. The decision of which opiate to use should be based on the prescriber's experience with the opiate and the preference of the child.

In opiate naïve the child should start on a standard starting dose of an immediate release (IR) preparation. Even if the opiate requirement is determined and a long acting opiate is commenced. The child may still experience breakthrough or incidental pain and require IR doses. Ensure constipation is avoided by a regular laxative when a child is commenced on Opiates.

- Long acting (modified release) opiates:

Once the opiate requirement has been established the child could start a long acting opiate. The drug of choice will depend on the breakthrough opiate used e.g. Oromorph (breakthrough pain) and MST (long- acting agent) as well as the preferred route and preference of the child.

- Morphine: MST or Zomorph (oral)
- Oxycodone: Oxycontin (oral)
- Fentanyl: Fentanyl patches (topical)
- Bupronorphine: BuTrans patches (topical)

- Opiate (IV/Subcut) infusions (e.g. Morphine, Diamorphine and Oxycodone) may be required especially if rapid pain controlled is required or gut absorption is poor. PCA(Patient controlled analgesia) may also be an effect means of pain control offering both a background Opiate dose and bolus sc/iv doses for breakthrough pain. PCA is offered in the community by both specialist palliative care services.

2. Anxiolytic

- Midazolam buccal for acute anxiety or longer-acting benzodiazepine e.g. Diazepam or Clonazepam may also be effective for frequent or persistent anxiety.
- Midazolam - (IV/Subcut)- Sedating and amnesic effect as well.
- Methotrimeprazine (levopromazine) – (Oral /IV/Subcut)

3. Anti-emetic

- Cyclizine – (Oral /IV/Subcut)
  May be 1st line if central element to nausea. It may also be given as a subcutaneous infusion using the total daily dose over 24 hours.
- Ondansetron – (Oral /IV/Subcut)
- Haloperidol -(Oral /IV/Subcut)
- Domperidone – (Oral)
- Methotrimeprazine (levomepromazine) – (Oral /IV/Subcut)
  If no response to cyclizine, but useful as can be given subcutaneously, and has additional anxiolytic effect. May cause some sedation as well.
- Dexamethasone may help with nausea.

4. **Cough**
   - Low dose long-acting Opiates e.g. Morphine (MST/Zomorph) or Oxycodone (Oxycontin) may relieve intractable cough.

5. **Dyspnoea**
   - Humidified oxygen may help.
   - Opiates (Morphine/Diamorphine/Oxycodone) may also help with dyspnoea.
   - Midazolam buccal for agitation or distress.
   - Dexamethasone (Oral /IV/Subcut) may help bronchospasm / airway obstruction.

6. **Respiratory secretions**
   - Hyoscine patches can help but a dry mouth is unpleasant, so good mouth care is essential.
   - Glycopyrronium(Oral /IV/Subcut) may also be useful.
     (tablets & oral liquid available on a named patient basis).

7. **Restlessness / confusion / hallucinations**
   - Haloperidol –(Oral /IV/Subcut)
   - Methotrimeprazine (Levomepromazine) – (Oral /IV/Subcut)
   - Midazolam (buccal) for acute agitation

8. **Syringe driver mixing and compatibility**
   See APPM Formulary or BNFc for more details.

Once the child has died

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

- The on-call doctor will need to confirm death. 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.

- Inform the on-call consultant immediately unless they are there anyway, which is inevitably the situation.

- The doctor will then need to write a medical certificate confirming the cause of death. It is often useful to also write a cremation form especially if the family are uncertain about their next steps. If the death is 'Unexpected' (this is most unlikely with an expected death of a CF patient) then discuss with the on-call consultant. A discussion may be required with the coroner before the medical certificate is written.

- 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 will discuss this with the family.

- The doctor or a member of the CF team must phone the GP and local paediatrician as soon as possible and record the time this is done in the notes.

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

- 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).

- Mandatory reporting. If a death is unexpected contact the local SUDI paediatricians - Dr Paul Hargreaves or Dr Kingi Aminu at Chelsea & Westminster Hospital. 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. The family will receive their child's 'Death certificate' from the council.

- 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 or a doctor who has cared for the child during their last illness, 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.

After care

1. Transport Home of a Child's Body from RBH

A child's body can be removed from the hospital at any time if it is an 'Expected' death. The family may wish for the child to go home, to a relative's house or to a hospice. The documentation of death by a doctor is called the 'Medical certificate'. The 'Death certificate' is the document issued by the Local Registry Office. According to the Child Death Review process all 'Unexpected deaths' should be discussed with the Coroner prior to any discussion or consideration about transfer of the body out of the hospital.

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. NB. London Ambulance Service DOES NOT perform this service

2. Bereavement support

- Parents will be invited (by letter) to come back to discuss any issues with a consultant 4-6 weeks after the child's death.
- Bereavement counselling is available to families at the Brompton or we can help the family access support in the community. .
- The CF team should signpost the family to local bereavement services. This can be supported by the specialist palliative care team.
- 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.

- Staff debrief should be offered for all involved. Additional support should be offered to staff as requested.

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 ORAL ANTIBIOTICS - PROPHYLACTIC DOSES

Oral

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.
Co-amoxiclav **400/57** (Augmentin duo)	Oral Susp	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. **Clean teeth after dose**	
Co-amoxiclav **125/31**	Oral Susp	<1 yr: 0.25ml/kg (max 5ml) bd		
Co-amoxiclav **250/62**	Oral Susp	1-<6 yrs: 2.5ml bd 6-12 yrs: 5ml bd		
Co-amoxiclav 250/125	Oral tabs	>6 yrs: 1x (375 mg) tab bd		
Flucloxacillin	Oral	3-5kg: 125mg bd 5-9kg: 175mg bd 9-15kg: 250mg bd Older children: 25 mg/kg bd (usual max 1 gm 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.***

11.1b ORAL ANTIBIOTICS – TREATMENT DOSES

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.

Azithromycin	Oral	10 mg/kg od max 500 mg NOTE dose differs from prophylactic and long term use	*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 and given immediately.	2-3 weeks

Ciprofloxacin	Oral	<1 month: 15 mg/kg bd ≥1month: 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	<8 kg - 7.5mg/kg bd 8 – 11kg – 62.5 mg bd 12 – 19kg – 125 mg bd 20 – 29kg – 187.5 mg bd 30 – 40kg – 250 mg bd (if >12 years old can increase to 500mg bd if necessary)	Cheaper alternative to azithromycin. Can cause tooth and tongue discolouration. Part of NTM protocol.	One month Care needed as interacts with some drugs e.g. itraconazole, rifabutin – check BNFc	

Co-amoxiclav **400/57** (Augmentin-Duo)	Oral susp	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	Co-amoxiclav 625mg tabs are to be used in preference to 2 x 375mg tabs to reduce clavulanic acid intake.	One month
Co-amoxiclav **250/62**	Oral Susp	1-<6 yrs: 5ml tds 6-12 yrs: 10ml tds			
Co-amoxiclav **500/125**	Oral tablets	>6 yrs: (625mg tabs) 1 tab TDS			
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	30-35 mg/kg TDS MAX 4 gms/day	Give 1 hour BEFORE meals or on an empty stomach. Liquid tastes awful – different brands may be tolerated better than others.	NOTE treatment dose now three times a day	One month
Fusidic acid	Oral	<1 yr: 15mg/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	<12 yrs: 10mg/kg (max 600mg) **tds.** ≥12 yrs: 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.		Two weeks
Minocycline	Oral	>12 yrs: 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. Check re oral contraceptive interactions. Can cause red staining of urine, tears and saliva.	Two weeks See appendix II.

11.1c INHALED ANTIBIOTICS

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 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 which tastes awful.
Aztreonam Lysine (Cayston) Homecare delivery	Nebulised	75 mg tds during alternate months Licensed >6 years	3rd Line Doses should be taken at least 4 hours apart. Pre dose with bronchodilator	***Consultant decision.*** Colistin or tobramycin usually given during the intervening month Reconstitute only with solvent provided.
Ceftazidime	Nebulised	1 gm bd Reconstitute 1 gram injection with 3ml water for injection	For *B cepacia*. Tastes awful.	***Consultant decision***
Colomycin® (Colistin) Homecare delivery	Nebulised (**not** via an I-Neb)	<8 yrs: 1,000,000 Units bd >8 yrs: 2,000,000 Units bd 1,000,000 units = 1 megaunit (Mu)	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.**	BNFc states 1 month to 2 yrs dose is 0.5-1Mu
Promixin® (Colistin) Homecare delivery	Nebulised via I-Neb	< 8 years: 500,000 units bd >8 years: 1,000,000 units bd See physiotherapy section 6.15c		

Colobreathe® turbospin (Colistin) Homecare delivery	Inhaled (dry powder inhaler)	1 capsule bd via Turbospin powder inhaler Licensed >6 years only	Doses should be inhaled as close as possible to 12 hours apart.	***Consultant decision*** Should be used as per NICE guidance criteria: Can be used if child will clinically benefit from continued colistin but does not tolerate it in its nebulised form and thus tobramycin therapy would otherwise be considered.
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 half dose colistin – 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® Homecare delivery	Nebulised	300 mg bd during **ALTERNATE MONTHS** Licensed >6 years only		***Consultant decision.*** Colistin will usually be given in the month off TOBI
Tobramcyin – TOBI Podhaler® Homecare delivery	Inhaled (dry powder inhaler)	112mg (4 x 28mg capsules) bd via podhaler during **ALTERNATE MONTHS** Licensed >6 years only		***Consultant decision*** Doses should be inhaled as close as possible to 12 hours apart and not less than 6 hours.

11.1d INTRAVENOUS ANTIBIOTICS

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 / co-amoxiclav.

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 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 1.5g 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	50 mg/kg tds (Max 2 gms tds).	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.
Colistin	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**)	Slow infusion over 30 mins. Max concentration is 40,000 units/ml. Boluses can be used for **Portacaths** only – not PICC lines. <12 yrs: dilute to 90,000 units/ml. ≥12 yrs: dilute to 200,000 units/ml. Measure renal function once a week.	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 (max 400 mg) 12 hourly for 3 doses (loading dose) followed by 10mg/kg (max 400 mg) od.	Can give as a slow bolus or infusion over 30 minutes	Glycopeptide	*Consultant decision*
Temocillin	IV	25mg/kg bd (Max dose 2g bd)	Slow bolus over 3 – 5 minutes	Penicillin	*Consultant decision*. 3rd line Dilution: water

Tigecycline	IV	> 12 years: 1mg/kg bd (max 50mg bd)	Infusion over 30 to 60 minutes. Nausea/vomiting a real problem. Use regular oral Ondansetron.	Tetracycline	Patients should be > 12 years old (due to discolouration of growing teeth/bone) Reserved for treatment of NTM – *consultant decision*.
Timentin (Ticarcillin/ Clavulanic acid)	IV	80 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 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. **DO NOT PRESCRIBE THIS DOSE FOR NON-CF CHILDREN.**

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	50 mg/kg	50 mg/kg
15 - 17	750 mg	750 mg
18 - 21	1.0 gram	1 gram
22 - 25	1.2 grams	1.2 grams
26 - 30	1.4 grams	1.4 grams
31 - 35	1.6 grams	1.6 grams
36 - 40	1.8 grams	1.8 grams
41 - 45	2.0 grams	2 grams
46 - 55	2.0 grams	2.5 grams
56 & above	2.0 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.

11.1e ANTIFUNGAL ANTIBIOTICS

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 6.9. 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. Headaches seem commonest problem but in theory hepatotoxic. Adrenal suppression also been seen when combined with budesonide. Do liver function tests if taken for longer than 1 month or if known liver dysfunction. Note interaction with rifampicin. See section 6.9 re levels.	See **section 6.9** for length of courses.
Posaconazole	Oral	>8 years: 400mg BD Monitor levels.	3rd line for Aspergillus/ABPA where patients have not responded to or are intolerant of itraconazole **and** voriconazole . ***Consultant decision* and funding required, preferably prior to initiation (not licensed in <18 years old).** Take dose immediately following a meal (preferably fatty meal) to enhance absorption. If this is not possible, may need to use 200mg QDS dosing. Levels should be monitored on initiation, on amendment of dosage, if an interacting drug is commenced or efficacy is not observed. Random sample taken after at least 1 week on therapy. Aim >0.7mg/l. Monitor liver function tests monthly. Levels reduced by ranitidine and proton pump inhibitors. Stop where possible. Note interaction with rifampicin.	

Voriconazole	Oral	**2 – 11 years:** 9mg/kg (max 350mg) bd (Liquid preferred) **12 - 14 years:** **<50kg** 9mg/kg (max 350mg) bd **>50kg** 400mg bd for 2 doses then 200mg bd (max 300mg bd). **15 years +:** **<40kg:** 200mg bd for 2 doses then 100mg bd (max 150mg bd) **>40kg**: 400mg bd for 2 doses 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 6.9. 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. Adrenal suppression has been reported in patients also taking inhaled corticosteroids. See section 6.9 for levels.	See **section 6.9** 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 the standard amphotericin preparation (fungizone) for IV use.	***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 od 3months - 1yr: 50 mg/m^2 od >1 yr: 70 mg/m^2 (max 70mg) on day 1 then 50 mg/m^2 (max 70mg) od. This can be increased to 70 mg/m^2 (max 70mg) od 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).	***Consultant decision.*** Infuse over 60 mins. Dilute to concentration not exceeding 500 mcg/ml with 0.9% sodium chloride. Incompatible with glucose solutions.

11.1f OTHER RESPIRATORY TREATMENTS

Aminophylline	IV	**Load:** 5mg/kg (max 500mg) over at least 20 minutes, then – **IV infusion:** <12 years: 1mg/kg/hour >12 years: 0.5 – 0.7mg/kg/hour	***Consultant decision***	Do not use loading dose if already receiving oral theophylline or aminophylline. Measure levels 4- 6 hours after starting infusion, and daily thereafter. Do not exceed 20mg/l. Care needed as interacts with some drugs e.g. clarithromycin, ciprofloxacin – check BNFc
Azithromycin (see 11.1a & 11.1b for standard antibiotic doses)	Oral	<15kg: 10mg/kg od 3/week 15-40 kg: 250 mg od 3/week >40kg: 500 mg od 3/week Mon/Wed/Fri	Potential long-term treatment as anti-inflammatory. ***Consultant decision***	*Potential* for hepato- and ototoxicity but usually *very* well tolerated. **Avoid** long term concurrent use with erythromycin
DNase (Dornase alpha) Homecare delivery	Nebulised	2.5 mg once daily Consideration of alternate day after 6 months if well or treatment burden an issue.	In afternoon, **at least 1 hour pre-physiotherapy.** Can be given at bedtime (see section 6.4).	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 DNase fails. For 3.5% solution: dilute 7% solution with an equal volume of water for injections

Ivacaftor Homecare delivery	Oral	6 years and above: 150mg bd	***Consultant decision*** For children with G551D mutation. Liver function tests 3 monthly for 1st year then yearly (annual review).	Take with fat containing food. Avoid food containing grapefruit or Seville oranges. See section 6.8 for specific drug interactions. Always check for interactions when initiating treatment with Ivacaftor or whenever new medicines are prescribed. Refer to the paediatric pharmacy team for information.
Mannitol Homecare delivery	Inhaled	Initiation dose assessment: see details in Summary of Product Characteristics on www.medicines.org.uk Therapeutic dose regimen: 400mg (10 x 40mg capsules) bd via inhaler supplied Licensed for >18 years only	***Consultant decision*** Not approved for use in children at RBHT, and funding should be sought before initiation of treatment	Doses should be taken morning and evening with evening dose taken 2 – 3 hours before bedtime.

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 established on pancreatic enzymes is *approximately* 1 capsule per 3-5 grams of fat.
- In babies, start with ½ scoop per feed (average fat content of 150ml standard infant milk is 5g) mixed with small amount of expressed breast milk, infant formula or apple puree*, just before feeds and increase in half scoop steps (quarters is too fiddly). Do not put Creon granules into the bottle.
- Enzymes may not be chewed or *mixed into* food, do not mix 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

***NOTE:** At RBH we use apple puree to provide enzymes from birth as the puree keeps the enterically coated enzyme spheres in a suspension. 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 as it contradicts the WHO and Department of Health recommendations on the age that solids should be introduced to infants.

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. 1ml of Paediatric Liquid contains 1,743 mcg of Vitamin A, 10mcg of vitamin D, 48mg Vitamin E, and 0.4mg of Vitamin K. One Softgel or 2 chewable tablets contains 5505mcg of Vitamin A, 20mcg of vitamin D, 180mg (softgel)/97mg (chewable tablets) Vitamin E, and 0.7mg of Vitamin K. All contain a number of other vitamins and trace elements, and have the advantage of containing both vitamin E and vitamin K. Note if aquadeks is spilt it can stain clothes yellow.

  We are now offering Aquadeks to all newborn screened children (including those who are pancreatic sufficient). If children will not tolerate it, then we will use standard dalivit and vitamin E. With experience, we may offer this to older children but we are not planning a sudden change for all our patients.

- Abidec: not usually given due to low vitamin A content however may be a suitable alternative if Dalivit unavailable

- One **vitamin A+D capsule BPC** contains – vitamin A 1200 mcg, vitamin D 10 mcg

- **Vita-E gel capsules**: 75 unit capsule ≈ 50 mg vitamin E
  400 unit capsule ≈ 268 mg vitamin E
  (Note that 200iu capsules no longer available from GPs)

Recommended dosing (empirical):

Birth to 1 year:

- Either **AquADEKs™** Paediatric Liquid 1ml od
  (= Vit A 1,743mcg, Vit D 10mcg, Vit E 48mg, Vit K 0.4mg)

- Or **Dalivit** 0.6 ml + **Vitamin E Liquid** 50 mg (0.5ml) od
  (= Vit A 1,500mcg,Vit D 10 mcg)

>1 to 4 years:

- Either **AquADEKs™** Paediatric Liquid 2ml od
  (=Vit A 3,485mcg, Vit D 20mcg, Vit E 96mg, Vit K 0.8mg)

- Or **Dalivit** 1.2 ml + **Vitamin E Liquid** 100 mg (1ml) od
  (= Vit A 3000mcg, Vit D 20 mcg)

>4- 8 years:

- Either **AquADEKs™** Paediatric Liquid 2ml od
  (=Vit A 3,485mcg, Vit D 20mcg, Vit E 96mg, Vit K 0.8mg)

- Or **Dalivit** 1.8 ml + **Vitamin E Liquid** 100 mg (1ml) od
  (= Vit A 4500mcg, Vit D 30 mcg)

> 8 years:

- Either 2-3 **Vitamin A&D capsules** (= Vit A 2400-3600mcg, Vit D 20-30mcg) + **Vitamin E (Vita-E Gel 75iu/400iu Caps)** 150 - 400iu.

- Or 1 - 2 **AquADEKs™ Softgels/ 2 - 4 Chewable tablets** od
  (= Vit A 5,505-11,010mcg, Vit D 20–40mcg, Vit E 97-360mg,
  Vit K 0.7-1.4mg)

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

Vitamin D deficiency (see section 8.4)

Any one with a vitamin D level below 50nmol/l should be treated.

Give oral colecalciferol 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 liquid 3000 units/ml. 10 mcg of colecalciferol is equivalent to 400 units.
- *or* colecalciferol 20,000 units capsules given three times a week – Mon, Wed & Fri;
- *or* colecalciferol 50,000 unit capsules given once a week.

Intramuscular calciferol preparation is an alternative -

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

Vitamin K

Offered to all children aged 6 years (including pancreatic sufficient) and mandatory for those with liver disease (with or without clotting abnormalities).

Use **water-soluble** preparation: **Menadiol phosphate** tablet. Tablet can be swallowed or dissolved.
- 6 years & above: 10 mg od.

Newborn screened children will receive a small amount of vitamin K from diagnosis contained within Aquadeks. If they do not tolerate aquadeks, we will wait until 6 years to start.

11.2c 'Antacids'

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

- **Ranitidine**: <1 month: 2 mg/kg tds (max 3 mg/kg tds)
  1 – 6 months: 1 mg/kg tds (max 3 mg/kg tds)
  >6 months: 2-4 mg/kg bd (max 150 mg bd)
  - small risk of headache.

- **Omeprazole**: 0.4-0.7 mg/kg bd (max 40 mg/day).

- To exceed this dose ie up to 1.5 mg/kg bd is a *consultant decision*.
- Round to nearest 2.5mg (quarter of a tablet) if using dispersible 'MUPS' tablets, for those that cannot swallow capsules/tablets whole.
- Tablet can be cut in half or quartered but should not be crushed or chewed. Do not try to give a fraction of a tablet by dispersing it – it does not disperse evenly!
- Allow tablet (or portion of) to dissolve on the tongue or disperse in water/juice/yoghurt and give the whole amount.
- Use capsules rounded to nearest 10mg if can swallow capsules whole.
- 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 (max 20mg) tds
  before the 1st and middle feeds of the day and last thing at night.

Plus

- **Omeprazole**: see above (11.2c) for doses

OR

- **Ranitidine** see above (11.2c) for doses

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 7.6.** 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

- **Polyethylene glycol (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 fruit cordial.
  - Can be given orally or via NG tube (usually latter) and 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**: 10 – 15mg/kg bd
  (can give total daily dose in 3 divided doses if necessary)
  - 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.

11.3 Home delivery of medicines

As a result of the introduction of the CF tariff, and also the supply arrangements for a number of new medicines i.e. TOBI® Podhaler, the use of homecare delivery for the supply of some medicines will become increasingly commonplace. This service will mean that certain medicines that are not able to be prescribed by the patient's GP, will be prescribed by the CF team at RBH, and then delivered directly to the patient at home by the hospital's chosen homecare provider, for as long as is required. This will start for new prescriptions in April 2014. The default for prescribing and supply of all medicines except the ones listed below should be from the GP in the first instance. However if the GP is not willing or able to prescribe, then the patient should be advised to contact a member of the paediatric CF team to arrange homecare delivery. The following medicines will automatically be supplied via homecare as soon as a patient is commenced on therapy: TOBI® Podhaler; Colobreathe®; Ivacaftor.

If homecare is required then please contact a member of the paediatric pharmacy team as soon as possible (Bleeps 7403/7410 or ext 4375) who will then advise on the process to be followed. The paediatric pharmacy team should also be informed if there are ANY CHANGES to patient medicines that are supplied via homecare i.e. dose changes or discontinuations. Where possible copy the paediatric pharmacist into correspondence detailing such changes.

Appendix I - Transition Integrated Care Pathway

TRANSITION OF CARE FROM THE PAEDIATRIC SERVICE TO THE ADULT SERVICE

Name: **Referring consultant:**

CRN or referring hospital:

Please attach a referral letter if outside the Royal Brompton Hospital.

Transition: Is the planned process of changing from paediatric family centred care to a more independent adult service. This process usually starts during the latter stages of paediatric care and ends in the early years of attendance in the adult service. It is a process that fully involves the young adult, their parents, and both the paediatric and adult Cystic Fibrosis (CF) teams.

INTEGRATED CARE PATHWAY

The aim of this document is to improve the process of transition from paediatric to adult care. Please see: www.rbht.nhs.uk/cf-transition/

Date ICP started: **Date ICP ended:**

This ICP will start in the paediatric CF service and end after transition to the adult CF service. It must be kept at the front of the medical notes throughout this time. Please initial and date the YES/NO boxes.

This ICP is for adolescents with CF who are 14-17 years old and planning their move to adult care. Transition from the paediatric to adult clinic may take place over a period of up to three years.

- Patients will be contacted by the paediatric nurse specialist with an appointment for both the Pre-transition and Transition clinics.
- Both paediatric and adult CF teams are informed of the dates.
- Information will be provided and arrangements made for patients and families in advance of the clinic.

a. 14th Birthday Letter sent: Yes ☐ No ☐

b. Pre-Transition Clinic Date .....//..... Attended: Yes ☐ No ☐

i. *If NO, action taken:*

c. Transition Clinic Date .....//..... Attended: Yes ☐ No ☐

i. *If NO, action taken:*

d. 1st Adult CF Clinic .....//..... Attended: Yes ☐ No ☐

i. *If NO, action taken:*

Please ensure that the Family & Social Information Form is attached before sending to the adult team

	PLANNING TRANSITION	YES	NO	VARIANCE AND/OR ACTION TAKEN
1	Has transition been discussed with the patient? Has transition been discussed with parents / caregiver? Are there any concerns?			If NO reasons why: If NO reasons why:
2	Has the patient been given a Family & Social Information form to complete?			If NO reasons why:
3	Has the form been returned			If NO reasons why:
4	Has the pre-transition ICP data been fully completed?			If NO reasons why:
5	Is the transition ICP available for the adult team to review?			If NO reasons why:
CLINICAL DATA				
6	Age at diagnosis: Presentation at diagnosis:			Genotype: 1: 2:
7	**CURRENT CLINICAL STATUS** Date of measurements: Height: cm Weight: kg BMI: Lung function: FEV_1: (%) FVC: (%) MEF 25-75: (%) SaO_2: %			
8	**INTRAVENOUS ACCESS** What type of access is usually used? Are there any problems associated with this (seen psychology)? Portacath: Date inserted: Type: **Any problems?**			

CLINICAL DATA		YES	NO	VARIANCE AND/OR ACTION TAKEN
9	Has fertility been discussed? What contraception advice has been given? Is the patient using contraception? If yes, type:			If NO reasons why:
10	Gastrostomy? Feeding regimen: Any problems? Pancreatic sufficient? Pancreatic insufficient?			If YES: Date inserted: Type: If YES reasons why: Enzyme treatment?
11	**Previously tried airway clearance techniques**	**Current technique / Sessions per day / Adherence issues / Other**		
12	**Exercise**	**Comments**		**Current regimen**
13	**MSK**	**Pain?**		**Problems / Comments**
14	Are there any incontinence issues?			If YES please comment:
15	Has transplantation been discussed?			Details of discussion:

	ORGANISMS	**Ever grown (YES/NO)?**	**Where grown (RBH, local?)**	**Date of first growth**	**Current**
	Please include eradication attempts - successful or not				
16	Staphylococcus aureus Haemophilus influenzae Pseudomonas aeruginosa Stenotrophomonas maltophilia Achromobacter xylosoxidans Burkholderia cepacia complex, type: MRSA Atypical Mycobacteria, type: Other bacteria Aspergillus fumigatus Other fungus				
17	**HOSPITALISATION** How many times in the last 12 months? Reasons for admission: No. of courses IV antibiotics: At home: In hospital:				
18	**Medication list (please include whether patient has tried DNase or HTS previously but stopped, with reasons why)**	**Dose**	**Frequency**	**Route**	
19	Any allergies?		If YES describe the reaction:		
20	**COMPLICATIONS** Oxygen therapy Haemoptysis Pneumothorax ABPA DIOS	**Details**			

	Liver disease Oesophageal varices CF Related Diabetes Arthropathy Severe small airways disease Other associated conditions			
21	Does the patient receive any form of outreach support?			If YES please provide further details:
22	Has the patient had involvement/support from social services?			If YES please provide further details:
23	Has there been a psychological assessment and handover?			If NO reasons why:
24	Is the patient taking part in any research trials?			If YES, which ones? Can the patient transition while taking part? Have alternative plans been made?
	Transition clinic	**YES**	**NO**	**Variance and action taken**
1	At the transition clinic, has the patient been given transition information?			If NO reasons why:
2	Have the patient and family met all the members of the adult team today?			If NO, who do they need to meet? Has this been arranged?
3	Have both teams met to discuss any problems and issues prior to clinic?			If NO reasons why:
4	Were treatment plans discussed?			Please give details.
5	Has the patient been asked if they would like to attend a second transition clinic?			If NO reasons why:
6	If they wish to, has a date been given?			Date:

7	Have family & patient visited Foulis ward?			If NO reasons why:
8	Have they received an appointment for an adult CF clinic?			Date of clinic: A, B or C clinic?

Follow up at adult clinic		YES	NO	Variance and action taken
1	Has the PortCF co-ordinator been informed of the move?			Date:
2	Was the patient seen in the appropriate A, B, or C clinic?			If NO reasons why:
3	Were current medical notes available for the consultation?			If NO reasons why:
4	Has the Annual Review co-ordinator been informed?			Date:

Paediatric Clinic - Form completed by: Date:

Adult Clinic - Form completed by: Date:

Please send a copy to (attaching a referral letter if outside the Royal Brompton Hospital):

Alan Peres/Susan Talbot – Clinical Nurse Specialists (cfhomecare@rbht.nhs.uk)

Dr Diana Bilton – Consultant Physician (d.bilton@rbht.nhs.uk)

Dr Nicholas Simmonds– Consultant Physician (n.simmonds@rbht.nhs.uk)

Department of Cystic Fibrosis
Royal Brompton Hospital
Sydney Street
London SW3 6NP

FAMILY & SOCIAL INFORMATION

We would be grateful if you could please complete this form as it helps the Adult CF Team get to know you before transition. Thank you.

YOUR FAMILY BACKGROUND

Parents names:

Siblings names and ages:

CF-Siblings names and ages:

Who do you live with?

CF in extended family –relationship names and ages:

Ethnic origin:

SOCIAL SUPPORT

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

EDUCATION

Sixth Form (GCSEs, A Levels, GVNQ)

College/University:

Career interest:

Special educational needs:

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

OTHER COMMENTS

CONTACT DETAILS

Your mobile phone number:

Your email address:

Your next of kin's mobile phone number:

Your next of kin's email address:

This is for you to complete and will be sent to the adult CF team

ALL ABOUT ME – please introduce yourself to the adult 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.

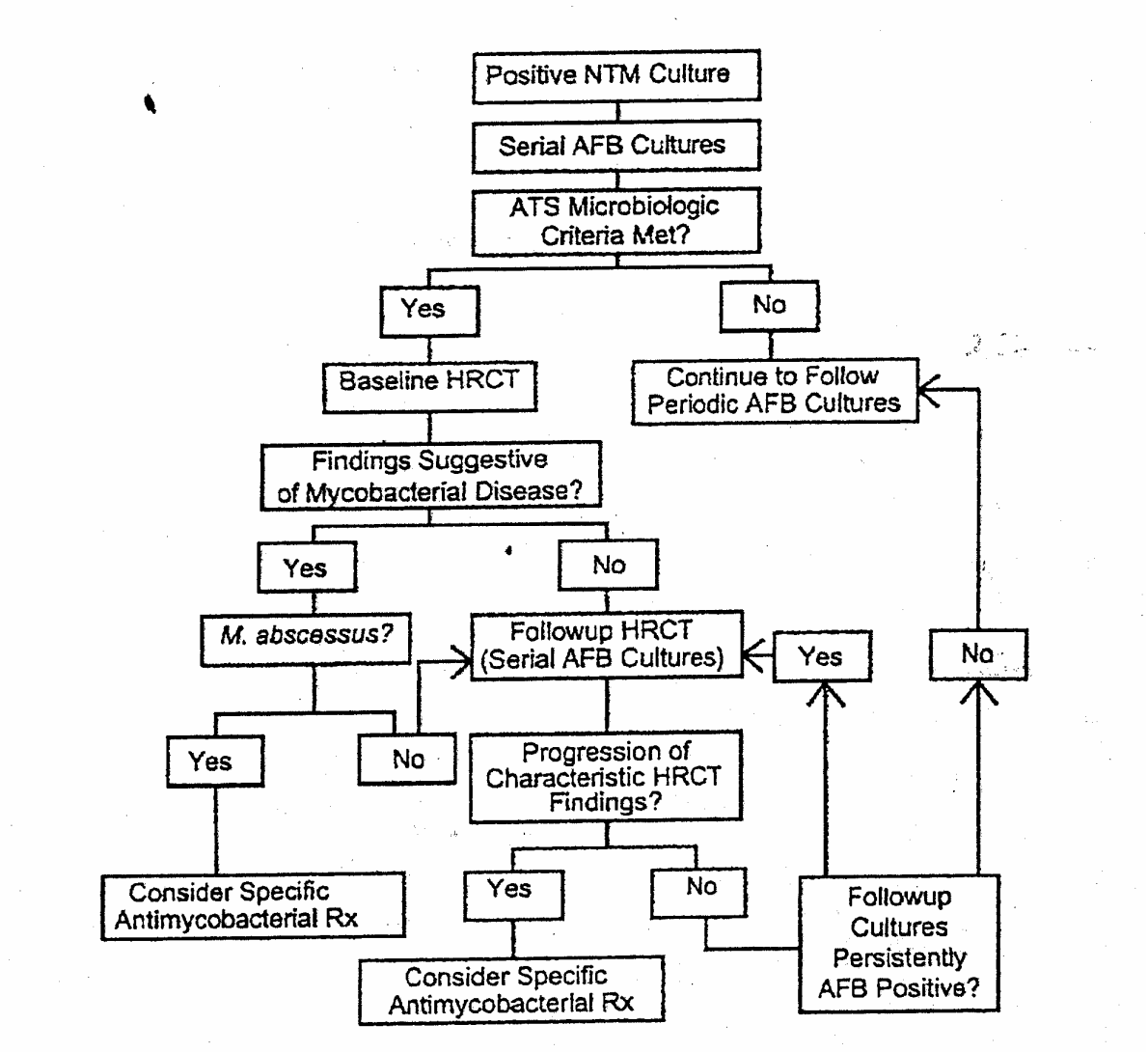
2. Indication for treatment of NTM

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 2 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 (2 weeks)	
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 (2 weeks)	
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.

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.

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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.

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
- Royal College of Ophthalmology document, revised in 2010 suggests that Ethambutol ocular toxicity is extremely rare in children. They recommend that screening for ocular side effects in children under 16 years not be performed. A baseline test however can be performed in children old enough to cooperate, refer to ophthalmologist at Chelsea & Westminster Hospital.
- 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 - Home visit report for Challenging CF Protocol

Name:	**Address:**
Dob:	
Hospital no:	
Date of visit:	**Telephone no:**
Name of Nurse performing visit:	
Name of Physiotherapist performing visit:	

Those at home at time of visit:

The Home: Flat/House/Garden
If flat: what floor? Lift: yes / no Stairs: yes / no
Immediate surroundings (i.e. busy road, trees, fields):
No of bedrooms:
Shared bedroom: yes/no

People living at home: 1. 4.
2. 5.
3. 6.

Pets:

Pets in the home:1. Pets living outside:1.
2. 2.
3. 3.

Other information

_____
_____
_____

Overall impression of home organisation:

Very organised Average Below average Very disorganised

Comments:_____
_____
_____

Allergen Exposure

Moulds

Evidence of damp	yes / no	details:
Evidence of mould on walls	yes / no	details:
Evidence of mould on windows	yes / no	details:

Other allergens/irritants:
i.e. air fresheners, poor ventilation, mouldy food, rodent infestations etc

_____
_____
_____

Smoke

Does Child smoke?	yes/no	
Do Parents smoke	yes / no	If yes; inside / outside
Other household members?	yes / no	
Do close friends smoke?	yes/no	
Evidence of smoke in home	yes / no	details:
Evidence of active smoking	yes / no	

Any known Allergies? yes / no Details:

Action required?

Medication

Current medication:

Antibiotics	Name	Dose	Frequency	Route	Available	In date
					Yes / no	Yes / no
					Yes / no	Yes / no
					Yes / no	Yes / no
Antifungal					Yes / no	Yes / no
					Yes / no	Yes / no
					Yes / no	Yes / no
					Yes / no	Yes / no
Vitamins					Yes / no	Yes / no
					Yes / no	Yes / no
					Yes / no	Yes / no
Anti-reflux					Yes / no	Yes / no
Other					Yes / no	Yes / no

Current Inhaled /nebulised Medication:

Name	Dose/Frequency	Route	Available	In date
			Yes / no	Yes / no
			Yes / no	Yes / no
			Yes / no	Yes / no
			Yes / no	Yes / no
			Yes / no	Yes / no
			Yes / no	Yes / no
			Yes / no	Yes / no

Nebuliser make:
Date of last nebuliser service:
Cleanliness of machine:
Correct cleaning/sterilization technique yes/no
Correct administration of nebulised medication yes/no
I-neb use: yes/no if yes assess computer data: result

Inhaler technique reviewed: yes/no comment:

Other medication previously used:

Medication location:
Spares available: yes / no / some
Appropriate devices: yes / no / some details:
Do parents supervise yes / no / sometimes
Inappropriate amount of un-used med (stockpiling) yes / no comment:
Prescription pick up rate: <50% / 50 -80% / >80%

Details of medications issues discussed:
(ie understanding of medication regime, knowledge of drug types, management of exacerbations etc)

Advice given:

_____
_____

Physiotherapy.

Airway clearance technique:

ACBT ☐ Positioning ☐ Manual Techniques ☐ AD☐ PEP MASK ☐ Pari PEP ☐ Flutter

☐ Acapella ☐ None ☐ Other ☐ Please specify…

Frequency :

Duration:

Other techniques tried:

Exercise:

Posture Assessment:

Assessment of stress urinary incontinence:

Other comments:

Nutritional Issues

Enzyme replacement therapy yes/no
Type: Dose:
Daily Routine of use (including at school):

Gastrostomy: yes/no
Feeding regimen:

Psychosocial issues

Previously identified issues yes / no
If yes give details:

_____
_____
_____

Appropriate perception of CF severity: yes / no
If yes give details:

_____
_____
_____

Psychosocial issues discussed at home visit:
(continue on separate page if necessary)

_____
_____
_____
_____
_____
_____

Referral to psychology made: yes / no

Plan:

1.

2.

3.

4.

Summary of home visit: **Signed:**

Appendix IV –

IVACAFTOR: PROFORM FOR COMMENCING / MONITORING TREATMENT

NAME..... DOB.....
HOSP NO..... GENDER M/F
G551D has been confirmed on printed report Y (if not, specimen to be resent)

PRE-DOSING DATA COLLECTION

Date.....
FEV1 ..... (L) ..... (%)
FVC ..... (L) ..... (%)
Weight ..... (kg)
Height ..... (cm)

Sweat test Date vol chloride
..../..... ...../.....
LIVER FUNCTION Date (must be within last 3 months) .....
ALT ..... (*normal range for each*)
AST .....
RENAL FUNCTION NORMAL Y/N

RECEIVING INTERACTING DRUGS? Y/N AGENT:

PRESCRIBED DOSE 150 mg bd Y/ other (reason):

CHECK WHEN DISCUSSED WITH PATIENT:

1. Potential drug interactions ☐
2. Take with fatty food ☐
3. Swallow whole/ do not chew ☐
4. Monitoring/ stopping criteria ☐

RESEARCH: OPTIONAL

1. Serum saved ☐
2. Urine saved ☐
3. Sputum obtained ☐
4. Lung clearance index performed ☐
5. Nasal brushing performed ☐
6. Nasal NO ☐

Interacting drug list

Azoles (itra/ vori/ poso)

Clarithro (not azithro)

Rifampicin

High dose steroids

Consultant: NAME .....

SIGNATURE .....

IVACAFTOR: PROFORM FOR COMMENCING / MONITORING TREATMENT

ON-TREATMENT MONITORING

DATE.....

NAME..... DOB.....
HOSP NO..... GENDER M/F

Month/ year started treatment.....

CURRENT DATA

FEV1 ..... (L) ..... (%)
FVC ..... (L) ..... (%)
Weight ..... (kg)
Height ..... (cm)

Sweat test Date vol chloride

TO BE DONE ONLY AT 1ST FOLLOW UP

LIVER FUNCTION
ALT .....
AST .....

RECEIVING INTERACTING DRUGS? Y/N AGENT:

PRESCRIBED DOSE -150 mg bd Y/ other (reason):

RE-CHECK:

1. Potential drug interactions ☐
2. Take with fatty food ☐
3. Swallow whole/ do not chew ☐

Interacting drug list
Azoles (itra/ vori/ poso)
Clarithro (not azithro)
Rifampicin
High dose steroids

Doctor: NAME .....

SIGNATURE .....

Appendix V - 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. You may want to send in the form by recorded delivery.

7. Keep a photocopy of completed form.

At 16 years of age when a child is in receipt of DLA they are usually contacted to complete the adult form. However now they will have to claim a PIP (Personal Independence Payment).

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.

Appendix VI - National Service Specification

(adopted 1.10.13)

NHS England

A01/S/b

2013/14 NHS STANDARD CONTRACT FOR CYSTIC FIBROSIS (CHILDREN)

PARTICULARS, SCHEDULE 2- THE SERVICES, A- SERVICE SPECIFICATIONS

Service Specification No.	A01/S/b
Service	Cystic Fibrosis (Children)
Commissioner Lead	
Provider Lead	
Period	12 months
Date of Review	

1. Population Needs

1.1 National/local context and evidence base

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting about 9,000 people (1 in 2,500 live births). It results from mutations affecting a gene that encodes for a chloride channel called the cystic fibrosis transmembrane conductance regulator (CFTR), which is essential for the regulation of salt and water movements across cell membranes. Absent or reduced function of CFTR results in thickened secretions in organs with epithelial cell lining hence it is multi-system, although mainly affects the lungs, digestive system and vas deferens.

The airways become clogged with thick sticky mucus, which impairs the clearance of microorganisms. This leads to recurrent infection, inflammation, bronchial damage, bronchiectasis and eventually death from respiratory failure. Patients are often infected with *Staphylococcus aureus* and *Pseudomonas aeruginosa* but also by a number of other organisms, some of which are resistant to many antibiotics.

In about 85% of cases the pancreatic exocrine ducts become sufficiently blocked to cause maldigestion and intestinal malabsorption (pancreatic insufficiency). Infants may fail to thrive and older children and adults may become under-nourished. About 15% of CF babies are born with a bowel blockage (meconium ileus) and some older patients develop recurrent blockages due to distal intestinal obstruction syndrome. Appetite is often adversely affected which is a problem as there is an underlying increase in metabolic demands leading to a need for an increased energy intake.

There are a number of other complications: most males are infertile; a high proportion of older patients will develop CF-related diabetes requiring multiple daily insulin injections; chronic liver disease and portal hypertension may develop; joints can be affected (CF-arthropathy) and with age bones can be affected by reduced bone mineral density; nasal polyps and sinusitis are not uncommon. Behavioral and psychological problems that are often associated with any severe long-term medical condition may also be present.

Cystic fibrosis mainly affects Caucasian populations. It is uncommon in people of Afro-Caribbean origin and other ethnic groups. The carrier rate of a CF gene mutation in the UK is 1 in 25 with an incidence of 1 in 2,500 live births. Median survival is currently 41.4 years (CF Registry 2010) and has been predicted to be at least 50 years for children born in 2000. However, the median age at death is currently 29 years and most people with CF who die each year are young adults, and occasionally some are children (3 in 2009).

2. Scope

2.1 Aims and objectives of service

Aim

The service aims to improve both life expectancy and quality of life for children with Cystic Fibrosis

Objectives

The service will deliver the aims of improving life expectancy and quality of life for children with CF by:

- Making timely diagnosis (including in response to newborn screening) with appropriate counselling and psychological support to the child and their family.
- Providing high quality proactive and preventative treatment and care to optimise lung function and nutritional status.
- Ensuring a safe, cost effective, high quality service for the recipients of the services commissioned.
- Ensuring equity of access to services for the CF population.
- Facilitating autonomy and transition from children's care to adult care and encouraging independent care.
- Supporting parents and families of children with CF, as well as the child.
- Supporting the child in helping them to manage their CF independently in order that they can aspire to a life less hindered by their condition and providing support to their families where appropriate.
- Ensuring effective communication between patients, families and the service providers.
- Providing a personal service, sensitive to the physical, psychological and emotional needs of the patients and their families.

This specification sets out the core elements of the service and standards by which CF services will be provided. Its purpose is not to define who the providers are. It defines the service to be provided and is supported by payment by results (PbR) currencies and funding streams. The specification will be used to define the models of care, agree the providers and establish robust shared care/network care arrangements where appropriate.

This service specification does not include generic healthcare services such as dental service, general practice services, ophthalmology services etc. required by individuals with CF which will be accessed in the same way as by the non-CF population. However, close liaison is vital between CF services and generic services and the CF service will have processes in place to ensure that communication takes place.

The providers of the service will demonstrate that they are meeting, or with the support of commissioners, are working towards meeting, the requirements of this service specification. Specialist CF Centres not currently meeting the specification will have a plan to do so by April 2014 which has been agreed with commissioners. Network care providers not currently meeting this specification will have a plan to do so by April 2016 which has been agreed with commissioners.

2.2 Service description/care pathway

The guiding principle within the service requirements is that all services will be provided in accordance with the CF Trust document "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011). Care is directed by a specialist centre.

All Services

As a minimum:

- Every CF specialist centre will have a Director who is responsible for the service
- Every individual will have a named CF consultant in accordance with section 3.1 of the CF Trust document "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011)
- The model of care must be governed by assurances of standards of care, access with care at home or close to home (where appropriate), and consistency and equity of access including the provision of home antibiotic services.
- Inpatient, day care, outpatient, diagnostic and homecare services will be co-ordinated to ensure continuity of care for the patient.
- Patients and their families will be seen in an age appropriate, comfortable environment, ensuring privacy, dignity and protection from cross infection.
- Patients and their families will be afforded the right to be fully informed of their condition, and to ensure that information is communicated in an understandable,

sympathetic and age appropriate manner.

- Patients and their families will be encouraged to participate in the planning of their care.
- Patients and their families will be made aware how to contact their clinical teams and cystic fibrosis support groups.
- Within the required timescales, complete and accurate data is submitted to the UK CF Registry subject to patient consent.

Specialist Care Responsibilities

Specialist centres will be responsible for providing the care plan for all patients. This includes the responsibility for determining when high cost drug (such as Dornase, Tobramycin, Colistimethate sodium and Aztreonamlysine) will be prescribed, in accordance with the national commissioning policy.

All specialist centres need to be fully operational and in a position to take referrals. Clearly defined links must be in place with community services and hospitals. Centres serving more rural areas must be able to demonstrate an ability to provide either network care or outreach care for children where appropriate.

All main centres will need a Service Manager with dedicated time and responsibility for the CF service.

Specialist centres must be able to provide cover for annual leave, study leave and long term absence (e.g. long term sickness or maternity leave) of centre staff.

The service must be able to provide for urgent care needs and advice 24 hours a day, 7 days a week. This will include management of emergencies such as haemoptysis, pneumothorax and bowel obstruction (including Distal Intestinal Obstruction Syndrome).

Telephone advice must be available. Clear contact numbers will be given to patients to enable them to obtain advice from the specialist team at any time. During out of hours contact, a process must be in place to ensure a clear line of communication with a CF specialist. The specialist centre will agree arrangements for 24 hour services with network clinics to ensure equity of access across a network service.

Network Care

Network care providers will typically have fewer numbers of patients than a specialist centre and so may have fewer staff. Care is therefore provided in partnership with the specialist CF centre that co-ordinates the network. Providers of network care for children will meet the requirements detailed in section 2.3 of the CF Trust document "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011).

As a minimum the network service will have:

- A local CF multi-disciplinary team meeting the standards detailed in

section 2.3 of the CF Trust document "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011).

- Regular locally run CF multi-disciplinary team out patient clinics some of which will be joint clinics with the specialist CF centre that co- ordinates the network. Each patient will be seen by the full specialist multi-disciplinary team at least twice /year, either in a joint clinic at the network centre or at the specialist centre.
- Inpatient facilities suitable for routine CF admissions.
- Ward nurses with sufficient CF experience.

Annual reviews will take place at the specialist CF centre (unless the Network CF Clinic can provide all recommended clinical reviews and investigations, in which case it may be done jointly by both teams in the local centre).

Network care providers must be able to comply with the standards specified below for CF inpatient care.

Network care providers must be able to provide cover for annual leave, study leave and long term absence (e.g. long term sickness or maternity leave).

Outreach Care

Outreach care differs from Shared/Network Care. Outreach care is provided by the specialist centre using the facilities of a local provider. Outreach care does not require the local provider to have any CF specialist staffing.

Outreach care can be provided for children where geographical constraint makes attendance at the specialist centre difficult. The full multi-disciplinary team will be present at outreach clinics.

Multi Disciplinary Approach to Specialist Paediatric CF Care

Care will be delivered by a multi-disciplinary team of trained, experienced, specialist healthcare professionals who routinely care for a critical mass of CF patients at a specialist centre. The levels of staffing within multi-disciplinary teams must be in line with the recommendations set out in section 3 of the Cystic Fibrosis Trust document "Standards for Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011).

General

All staff working within the CF service have an obligation to undertake continuing education and training to ensure updating of knowledge and skills. Core members of the CF multi-disciplinary team will be members of, and regularly contribute to, their relevant specialist interest group. Attendance at National/International specialist conferences will be demonstrable. It is recognised that not all staff will be able to attend every meeting every year; therefore the service will be able to demonstrate that there are internal mechanisms for feedback

to the multi-disciplinary team.

Each member of each professional group must demonstrate continuing professional development (CPD) in CF.

The service will ensure that processes are in place to ensure adequate workforce planning.

The service will be able to demonstrate that an appraisal process is in place for all staff.

Study days and network meetings will be run by the service for core and wider workforce teams.

Regular audit of services must be performed. Specific audits may be requested by the commissioner. Participation in research studies is encouraged.

There will be clear succession planning for staffing to ensure continuity of care into the future.

Each professional group will be required to meet the minimum competencies defined within section 3 of the Cystic Fibrosis Trust "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011) and the defined care pathway. In particular the following will be achieved:

Composition of multi-disciplinary team

Service Clinical Director/Lead CF Consultant

The consultant in charge of the paediatric service must have a certificate of training (CCT) in paediatrics with accreditation in paediatric respiratory medicine or equivalent in cumulative experience. He/she must also have at least three years experience working as a consultant in an accredited paediatric CF centre. He/she must be able to demonstrate active participation and attendance at national/international meetings and have a track record in teaching, audit and research. He/she must engage in the management of the service as a whole ensuring leadership of the multidisciplinary team and clinical governance of the service.

Cystic Fibrosis Nurse Specialists

CF Nurse Specialists must meet the standards identified in the CF Trust document "National Consensus Standards for the Nursing Management of Cystic Fibrosis" May, 2001.

Nurse Specialists will be members of the UK Cystic Fibrosis Nursing Association and must work within a CF multidisciplinary team.

All nurse specialists must be registered with the Nurses and Midwives Council and

those working with children must have undergone specific paediatric training.

Physiotherapists

Specialist CF Physiotherapists must meet the standards identified in the Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF) document "Physiotherapy National Standards of Care for people with Cystic Fibrosis 2011". They will be members of the ACPCF special interest group.

Dieticians

Specialist CF Dieticians meet the standards defined in Nutritional Management of Cystic Fibrosis (April 2002) and will be members of the UK Cystic Fibrosis Nutrition Group.

Medical Staffing

Specialist Consultants must have had training in a recognised CF Centre. They must be able to demonstrate active participation and attendance at national/international meetings and have a track record in teaching, audit and research. Specialist Consultants will also have CCT in paediatrics with accreditation in paediatric respiratory medicine.

Middle grade medical support will in most instances comprise a Trainee in paediatric respiratory medicine but may include a non- career grade with appropriate experience.

Pharmacists

Pharmacists must be registered with the General Pharmaceutical Council and be a member of the Cystic Fibrosis Pharmacists Group. Pharmacists' practice will reflect Pharmacist Standards in Cystic Fibrosis Care 2011.

Clinical Psychologists

Clinical Psychologists must be registered with the Health and Care Professions Council and be a member of the UK Psychosocial Professions in CF Group (UKPPCF).

Social Workers

Social Workers must be registered with the Health and Care Professions Council and be a member of the UK Psychosocial Professions in CF Group (UKPPCF).

Provision of Care

Annual Review

A full review must be undertaken by the specialist centre once a year, in line with the

standards defined in The CF Trust document "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011)

A personal care plan must be produced by a consultant and agreed with the patient as a result of every annual review undertaken.

Outpatient Care

Routine appointments should be every 2 to 3 months when stable and more often if not. The outpatient clinics are multidisciplinary with all patients being reviewed by the doctor and a CF nurse specialist, a physiotherapist and dietician at all routine reviews. There should be access to psycho-social support.

Inpatient Care

Beds in a ward suitable for cystic fibrosis care must be available within 24 hours for an emergency admission, as well as capacity to ensure elective and urgent admissions can be managed appropriately. There must not be a delay of more than one week of the proposed admission date for a routine/planned/elective course of treatment.

Inpatient facilities will meet the standards defined in the Cystic Fibrosis Trust "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011).

In particular, inpatients will:

- be entitled to and receive physiotherapy treatment 7 days a week if appropriate,
- have access to a specialist CF dietetic input at least twice a week, and more frequently if clinically appropriate,
- be seen by a CF consultant at least twice a week, and have access to consultant advice,
- be seen every day by a member of the medical team and have access to a Middle Grade doctor who is formally linked to the CF service,
- have access to a CF nurse specialist,
- have access to education facilities and support for school/college and examinations as appropriate,
- have access to appropriate play and recreational facilities 7 days a week,
- have provision for appropriate vascular access available at all times,
- have facilities for sedation for procedures (e.g. line insertion) available at all times,
- have access to facilities for exercise.

Every CF patient will be in their own room, with en-suite facilities to minimise the risk of cross infection and to enable them to continue life as normally as possible.

Patients must be admitted to wards that are familiar with the care and management of children with this condition and have developed the required expertise.

Nurses on the inpatient wards require specific expertise, and be committed to the CF service, with regular input and training from the specialist CF nurses. Patients will be admitted to a ward staffed by CF specialists or to wards that are familiar with the care and management of individuals with this condition and have developed the required expertise.

Provision will be made for inpatients to have a choice of food including high energy options and access to high energy mid meal snacks and drinks. This must include evenings and weekends.

IV Antibiotics

The service must have the ability to commence IV antibiotics on any day of the week.

An urgent course of treatment will be implemented within a maximum of 24 hours of the clinical decision being made.

There must not be a delay of longer than one week of the proposed admission date for a routine/elective/planned course of treatment.

Where appropriate, IV antibiotics may be provided at home, following receipt of the initial dose at the specialist CF centre or network care hospital.

Homecare

The life long multi-system nature of cystic fibrosis means that a complex regimen of home treatment is often recommended. Many patients and families require regular and consistent outreach from community services to support them in this care. This will include:

- Support in the community by the specialist CF multi- disciplinary team.
- Open access to nursing care in the community. This may be a CF nurse specialist from the CF service, or local Community nurses including children's nurses who have specific training, experience and supervision in CF.
- Patients undertaking home IV antibiotic therapy will have a formal assessment of suitability. This will include formal training and an assessment of competency of the patient and their carers in administering the IVs as well as the suitability of the home environment. There must also be planned review and assessment by the prescribing physician to ensure efficacy of each course of home IV antibiotics.
- Support for patients receiving overnight enteral feeding.
- Care of indwelling vascular access devices, gastrostomies and other stoma.
- Physiotherapy input where appropriate.
- Liaison with nurseries, school or college for patients still in education.
- Support through times of change in an individual's health including introduction of treatment for diabetes or home oxygen therapy and end of life care.

Where clinically appropriate home treatment is encouraged.

Outpatient and Day Case Facilities

The service will ensure that the facilities are available to support the best quality CF service allowing seamless care between the home and hospital. Thus patients can be seen routinely in an outpatient facility but there must be provision for urgent review and providing the first dose of an antibiotic course either in the outpatients or a day case facility or ward.

The facilities must take the need for infection control into consideration and demonstrate compliance with section 4.1 of the Cystic Fibrosis Trust "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011) when providing facilities for annual reviews, treatment, day case etc. This will include ensuring that CF patients are not kept waiting in communal waiting areas and that they remain segregated from each other at all times so as to minimise the risk of cross infection.

Equipment

The service will ensure that all relevant equipment is available, maintained and kept up to date in order that patients can receive and make use of appropriate equipment as well as treatment. In particular, the service will ensure that the following equipment is available as required:

The service will ensure that there is access to the provision of high quality spirometry (i.e. meeting UK/EU standards) for all appropriate patients. Access will be available to the home care team to enable the monitoring of selected patients in the home with oxygen saturation monitors and home spirometry.

Patients who need home oxygen therapy will receive timely assessment and prescription of oxygen according to the National Home Oxygen service.

Individual patients will have access to a range of clinically appropriate airway clearance devices.

There will be a comprehensive nebuliser service, which aims to provide devices that deliver drugs in a fast and efficient manner. The service will also be able to provide a range of mechanical devices required to provide intermittent positive pressure breathing and non- invasive ventilation where needed.

Individual patients will have access to blood sugar monitors and continuous glucose monitoring systems (CGMS). Inpatient access to enteral feeds, feeding pumps, nasogastric (NG) tubes, percutaneous endoscopic gastrostomy (PEG) tubes and gastrostomy buttons.

GPs will provide NG tubes, feeds and feeding pumps and giving sets for enteral feeding through an approved/agreed contractor or local community nursing service.

Diagnostics

The service will have access to all appropriate specialist CF diagnostic services, including:

- A microbiology laboratory that meets the 'Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis. First edition. September 2010.' and that routinely cultures for recognised CF pathogens such as Burkholderia cepacia complex and also performs tobramycin levels.
- Specialist radiology services, including contrast GI studies for bowel obstruction, ventilation perfusion scans, CT thorax, angiography, specialist liver scans, dual energy X-ray absorptiometry (DXA) bone scans and interventional services.
- A laboratory that performs specialist biochemical analysis such as faecal elastase and complies with the Association for Clinical Biochemists guidelines on performance 2003 of sweat tests.
- Specialist lung function laboratory that will test patients as well as provide support and training for those staff performing spirometry in the clinic setting.
- Epithelial ion transport testing (where required this facility will be available by collaborative arrangements with an appropriately equipped specialist CF Centre).
- Facilities to undertake bronchoscopy.

Other aspects of Paediatric CF Specialist Care

Diabetes Care

Management of CF related diabetes will be in accordance with the document 'Management of Cystic Fibrosis-related Diabetes Mellitus (2004)'. In particular:

- There will be joint management between the CF multi-disciplinary team and a diabetes specialist experienced in the management of CF related diabetes (CFRD).

The provider must have a documented protocol which describes how CFRD will be identified. The provider will undertake an annual audit which demonstrates compliance with the protocol.

Transitional Care

Transition from paediatric to adult care is the norm for all patients.
Transition will be planned with the patient and their parent(s)/carer(s) with due regard to patient choice. There should be an underlying assumption that transition is natural and expected. All parents/carers will be made aware as early as possible that transition into adult services will take place.

Arrangements for transition to adult services will commence from the age of 12 years and will be completed by the age of 18, when responsibility for care transfers to the specialist adult cystic fibrosis centre. The specialist paediatric cystic fibrosis centre responsible for the care of the child will be responsible for ensuring that transition arrangements are put in place for each child. It is particularly important that these

arrangements are carefully co-ordinated where the patient has had the majority of their care provided at a paediatric network clinic.

Every specialist paediatric CF service will have a formal policy for transition that is agreed with all specialist adult CF services to which their patients transfer.

The specialist paediatric CF centre will ensure the following:

- Early discussion with the patient and carers about the process of transition. Options for adult care will be detailed. The age for transition will be flexible but agreed 2-4 years in advance, with the intention to complete before 18th birthday.
- Notification to the adult centre of intention to proceed with transition.
- Copies of letters and the annual review report are provided to the adult centre at least in the year prior to the anticipated transition clinic.
- There is documented paediatric and adult multi-disciplinary team member liaison, involving all multi-disciplinary team groups.
- There is the opportunity to visit the adult centre, to meet key multi-disciplinary team members and view both IP and OP facility. Such a visit could be repeated if requested.
- There is a joint clinic with detailed clinical handover.

Specialist adult CF centres will demonstrate that they are actively engaging in the transition process for each child via an annual audit report to commissioners of the experience of patients who transitioned during the year.

Surgery

The decision to undertake surgery for patients with CF must be made jointly between the relevant surgeon, the CF clinicians and the child and their parents or carers. Acute admissions for acute abdominal pain will be managed by the CF team, in collaboration with other relevant clinicians. Where possible, surgical procedures should be undertaken at a hospital which also provides a CF service. If this is not possible, full access to CF specialists must be available to ensure that the child's CF needs are fully taken into account, including during any post operative period of inpatient care. A clear care plan must be developed, with regular contact and review between the relevant parties.

The surgical units must have a protocol or guideline relating to children with CF which has been developed in collaboration with the CF service. This protocol will specify required standards of cross infection control and dietary/physiotherapy support.

General anaesthetic must be undertaken by a paediatric anaesthetist with experience of CF, and conducted within appropriate facilities in accordance with the Royal College of Surgeons' publication regarding quality standards for paediatric surgery; Surgery for Children; Delivering a First Class Service (2008).

The surgical service must have access to a CF clinician, to ensure communication regarding any surgical procedure, before during and after the procedure.

Transplantation

When the possibility of transplantation is appropriate, it will be discussed with the child and family as early as possible. Access to information will be readily available to patients and their families.

Referral to the transplant centre for further assessment, if appropriate, will be made as soon as potential candidacy has been assessed.

Work up for transplantation will be undertaken in line with the guidance, processes and pathways defined by the transplant centre.

Palliative Care

Centres will demonstrate:

- Good working relationships with and access to the general palliative care team attached to the hospital/local hospice/local community team and their involvement in all such patients.
- Clear documentation of End of Life discussions.
- Access to bereavement support for patients.
- Clinical review and debrief following a patient death.

Infection Control

The service must have an infection control policy in place which demonstrates compliance with section 4.1 of the Cystic Fibrosis Trust "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011).

Clinical Governance

Clinical Governance will be demonstrated via:

- Microbiological surveillance to identify infection control issues and use of particular antibiotics.
- Proportion of patients with chronic Pseudomonas infection.
- Monitoring of lung function (FEV1) and rate of decline.
- Body Mass Index (as a percentile for children).
- Reviews of all deaths.
- Benchmarking with other similar centres, including use of the UK CF Registry data when available.
- Number and resolution times of complaints.
- Departmental risk register.

General Paediatric Care

When treating children, the service will additionally follow the standards and criteria outlined in the Specification for Children's Services (attached as Annex 1 to this Specification).

2.3 Population covered

The service outlined in this specification is for patients ordinarily resident in England*; or otherwise the commissioning responsibility of the NHS in England (as defined in *Who Pays?: Establishing the responsible commissioner* and other Department of Health guidance relating to patients entitled to NHS care or exempt from charges).
* - Note: for the purposes of commissioning health services this EXCLUDES patients who, whilst resident in England are registered with a GP Practice in Wales, but INCLUDES patients resident in Wales who are registered with a GP Practice in England.

The Provider shall provide paediatric services for patients with cystic fibrosis. Paediatric services shall be provided for patients up to the age of 18.

2.4 Any acceptance and exclusion criteria

Referrals can come from a number of sources, following the identification of a patient with suspected CF. These will include:

- Antenatal diagnosis of CF.
- A newborn screening result that suggests a high likelihood of CF.
- Clinical suspicion by a general paediatrician, GP or other hospital specialist.
- Neonatal diagnosis of meconium ileus.

Diagnostic services will be provided for patients suspected of having cystic fibrosis. Following referral with suspected CF, the service will be responsible for:

- Investigations leading to a rapid and clear diagnosis, where possible.
- Appropriate counselling of patients/parents.
- Early introduction of required treatment.

For the purposes of this specification, a cystic fibrosis patient is defined as:

- Having a confirmed or strongly suspected diagnosis of cystic fibrosis, which includes:
  - A compatible clinical history, supported by one or more of the following:
    - A positive sweat test
    - Two known disease forming CF gene mutations
    - Evidence of functional epithelial ion transport abnormality

2.5 Interdependencies with other services

There is no requirement for co-location with other services

The service will provide access or referral to specialists within:

- Endocrinology, including diabetes (with an interest in CF related diabetes), with joint clinics available on a regular basis,

- Hepatology,
- Gastroenterology,
- Rheumatology,
- ENT,
- Vascular services,
- Thoracic surgery,
- Palliative care,
- Clinical genetics,
- Transplantation services,
- Psychiatry,
- Paediatric Surgery,
- Gynaecology,
- Renal services,
- Anaesthetic services,
- Gastro-intestinal surgery,
- Pre-natal and new-born screening services.

If not available at a network care centre, processes must be in place to demonstrate clear pathways including Out of Hours/Emergency Care.

3. Applicable Service Standards

3.1 Applicable national standards e.g. NICE, Royal College

The services within this specification will be provided with reference to the following publications:

- The CF Trust document "Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK" (2011)
- National Consensus Standards for the Nursing Management of Cystic Fibrosis. May 2001.
- Nutritional Management of Cystic Fibrosis. April 2002.
- Association of Chartered Physiotherapists in Cystic Fibrosis document "Physiotherapy National Standards of Care for people with Cystic Fibrosis 2011"
- Clinical Care Pathway
- Management of Cystic Fibrosis-related Diabetes Mellitus (2004)
- Department of Health National Definition Set for Cystic Fibrosis (2009)
- Standards of care for patients with cystic fibrosis: A European consensus
- Pharmacist Standards in Cystic Fibrosis Care 2011

These standards may change over time and as required, the service specification and service level agreements will be updated to reflect such changes.

The service will meet and maintain national quality standards and any other national quality requirements that may from time to time be specified including multi-disciplinary Peer Review.

- Hepatology,
- Gastroenterology,
- Rheumatology,
- ENT,
- Vascular services,
- Thoracic surgery,
- Palliative care,
- Clinical genetics,
- Transplantation services,
- Psychiatry,
- Paediatric Surgery,
- Gynaecology,
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4. Key Service Outcomes

Annual Median Survival of the CF Cohort	
Body Mass Index (BMI)	Median BMI percentiles in age categories
Forced Expiratory Volume in 1 second (FEV1)	Number of patients and % with FEV1 >85% by age group and sex
Data Input	Number of complete annual data sets taken from verified data set expressed as a % of actual patient numbers
	Number of newborn screened patients since last data set
Pseudomonas (PA) Chronic PA is 3+ isolates between two annual data sets	Number and % of patients with Chronic PA infection on inhaled antibiotics by age group
Macrolides	Number and % of patients on chronic macrolide with chronic PA infection
	Number and % of patients on chronic macrolide without chronic PA infection

ANNEX 1 TO SERVICE SPECIFICATION:

PROVISION OF SERVICES TO CHILDREN

Aims and objectives of service

This specification annex applies to all children's services and outlines generic standards and outcomes that would fundamental to all services.

The generic aspects of care:
The Care of Children in Hospital (Health Service Circular (HSC) 1998/238) requires that:

- Children are admitted to hospital only if the care they require cannot be as well provided at home, in a day clinic or on a day basis in hospital.
- Children requiring admission to hospital are provided with a high standard of medical, nursing and therapeutic care to facilitate speedy recovery and minimize complications and mortality.
- Families with children have easy access to hospital facilities for children without needing to travel significantly further than to other similar amenities.
- Children are discharged from hospital as soon as socially and clinically appropriate and full support provided for subsequent home or day care.
- Good child health care is shared with parents/carers and they are closely involved in the care of their children at all times unless, exceptionally, this is not in the best interest of the child; Accommodation is provided for them to remain with their children overnight if they so wish.

Service description/care pathway

All paediatric specialised services have a component of primary, secondary, tertiary and even quaternary elements.

The efficient and effective delivery of services requires children to receive their care as close to home as possible dependent on the phase of their disease.

Services should therefore be organised and delivered through "integrated pathways of care" (*National Service Framework for children, young people and maternity services* (Department of Health (DOH) & Department for Education and Skills, London 2004)

Interdependencies with other services

All services will comply with Commissioning Safe and Sustainable Specialised Paediatric Services: A Framework of Critical Inter-Dependencies – DOH

Imaging

All services will be supported by a 3 tier imaging network ('Delivering quality imaging services for children' DOH 13732 March2010). Within the network;

- It will be clearly defined which imaging test or interventional procedure can be performed and reported at each site.
- Robust procedures will be in place for image transfer for review by a specialist radiologist, these will be supported by appropriate contractual and information governance arrangements.
- Robust arrangements will be in place for patient transfer if more complex imaging or intervention is required.
- Common standards, protocols and governance procedures will exist throughout the network.
- All radiologists, and radiographers will have appropriate training, supervision and access to Continuing Professional Development (CPD).
- All equipment will be optimised for paediatric use and use specific paediatric software.

Specialist Paediatric Anaesthesia

Wherever and whenever children undergo anaesthesia and surgery, their particular needs must be recognised and they should be managed in separate facilities, and looked after by staff with appropriate experience and training.[1] All UK anaesthetists undergo training which provides them with the competencies to care for older babies and children with relatively straightforward surgical conditions and without major co-morbidity. However those working in specialist centres must have undergone additional (specialist) training[2] and should maintain the competencies so acquired[3] *. These competencies include the care of very young/premature babies, the care of babies and children undergoing complex surgery and/or those with major/complex co-morbidity (including those already requiring intensive care support).

As well as providing an essential co-dependent service for surgery, specialist anaesthesia and sedation services may be required to facilitate radiological procedures and interventions (for example MRI scans and percutaneous nephrostomy) and medical interventions (for example joint injection and intrathecal chemotherapy), and for assistance with vascular access in babies and children with complex needs such as intravenous feeding.

Specialist acute pain services for babies and children are organised within existing departments of paediatric anaesthesia and include the provision of agreed (hospital wide) guidance for acute pain, the safe administration of complex analgesia regimes including epidural analgesia, and the daily input of specialist anaesthetists and acute pain nurses with expertise in paediatrics.

*The Safe and Sustainable reviews of paediatric cardiac and neuro- sciences in England have noted the need for additional training and maintenance of competencies by specialist anaesthetists in both fields of practice.

References

1 Guidelines on the Provision of Anaesthetic Services (GPAS) Paediatric anaesthetic services. Royal College of Anaesthetists (RCoA) 2010 www.rcoa.ac.uk
2 Certificate of Completion of Training (CCT) in Anaesthesia 2010
3 CPD matrix level 3

Specialised Child and Adolescent Mental Health Services (CAMHS)

The age profile of children and young people admitted to specialised CAMHS day/in-patient settings is different to the age profile for paediatric units in that it is predominantly adolescents who are admitted to specialised CAMHS in-patient settings, including over-16s. The average length of stay is longer for admissions to mental health units. Children and young people in specialised CAMHS day/in-patient settings generally participate in a structured programme of education and therapeutic activities during their admission.

Taking account of the differences in patient profiles the principles and standards set out in this specification apply with modifications to the recommendations regarding the following:

- Facilities and environment – essential Quality Network for In-patient CAMHS (QNIC) standards should apply (http://www.rcpsych.ac.uk/quality/quality.accreditationaudit/qnic1.aspx)
- Staffing profiles and training - essential QNIC standards should apply.
- The child/ young person's family are allowed to visit at any time of day taking account of the child / young persons need to participate in therapeutic activities and education as well as any safeguarding concerns.
- Children and young people are offered appropriate education from the point of admission.
- Parents/carers are involved in the child/young persons care except where this is not in the best interests of the child / young person and in the case of young people who have the capacity to make their own decisions is subject to their consent.
- Parents/carers who wish to stay overnight are provided with accessible accommodation unless there are safeguarding concerns or this is not in the best interests of the child/ young person.

Applicable national standards e.g. NICE, Royal College

Children and young people must receive care, treatment and support by staff registered by the Nursing and Midwifery Council on the parts of their register that permit a nurse to work with children (Outcome 14h *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010):

- There must be at least two Registered Children's Nurses (RCNs) on duty 24 hours a day in all hospital children's departments and wards.
- There must be an Registered Children's Nurse available 24 hours a day to advise

on the nursing of children in other departments (this post is included in the staff establishment of 2RCNs in total).

Accommodation, facilities and staffing must be appropriate to the needs of children and separate from those provided for adults. All facilities for children and young people must comply with the Hospital Build Notes *HBN 23 Hospital Accommodation for Children and Young People* NHS Estates, The Stationary Office 2004.

All staff who work with children and young people must be appropriately trained to provide care, treatment and support for children, including Children's Workforce Development Council Induction standards (Outcome 14b *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010).

Each hospital who admits inpatients must have appropriate medical cover at all times taking account of guidance from relevant expert or professional bodies (National Minimum Standards for Providers of Independent Healthcare, Department of Health, London 2002)."Facing the Future" Standards, Royal College of Paediatrics and Child Health.

Staff must carry out sufficient levels of activity to maintain their competence in caring for children and young people, including in relation to specific anaesthetic and surgical procedures for children, taking account of guidance from relevant expert or professional bodies (Outcome 14g *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010).

Providers must have systems in place to gain and review consent from people who use services, and act on them (Outcome 2a *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010). These must include specific arrangements for seeking valid consent from children while respecting their human rights and confidentiality and ensure that where the person using the service lacks capacity, best interest meetings are held with people who know and understand the person using the service. Staff should be able to show that they know how to take appropriate consent from children, young people and those with learning disabilities (Outcome 2b) (*Seeking Consent: working with children* Department of Health, London 2001).

Children and young people must only receive a service from a provider who takes steps to prevent abuse and does not tolerate any abusive practice should it occur (Outcome 7 *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010 defines the standards and evidence required from providers in this regard). Providers minimise the risk and likelihood of abuse occurring by:

- Ensuring that staff and people who use services understand the aspects of the safeguarding processes that are relevant to them.
- Ensuring that staff understand the signs of abuse and raise this with the right person when those signs are noticed.
- Ensuring that people who use services are aware of how to raise concerns of abuse.
- Having effective means to monitor and review incidents, concerns and complaints

that have the potential to become an abuse or safeguarding concern.

- Having effective means of receiving and acting upon feedback from people who use services and any other person.
- Taking action immediately to ensure that any abuse identified is stopped and suspected abuse is addressed by:
  - having clear procedures followed in practice, monitored and reviewed that take account of relevant legislation and guidance for the management of alleged abuse
  - separating the alleged abuser from the person who uses services and others who may be at risk or managing the risk by removing the opportunity for abuse to occur, where this is within the control of the provider
  - reporting the alleged abuse to the appropriate authority
  - reviewing the person's plan of care to ensure that they are properly supported following the alleged abuse incident.
- Using information from safeguarding concerns to identify non-compliance, or any risk of non-compliance, with the regulations and to decide what will be done to return to compliance.
- Working collaboratively with other services, teams, individuals and agencies in relation to all safeguarding matters and has safeguarding policies that link with local authority policies.
- Participates in local safeguarding children boards where required and understand their responsibilities and the responsibilities of others in line with the Children Act 2004.
- Having clear procedures followed in practice, monitored and reviewed in place about the use of restraint and safeguarding.
- Taking into account relevant guidance set out in the Care Quality Commission's Schedule of Applicable Publications
- Ensuring that those working with children must wait for a full CRB disclosure before starting work.
- Training and supervising staff in safeguarding to ensure they can demonstrate the competences listed in Outcome 7E of the Essential Standards of Quality and Safety, Care Quality Commission, London 2010

All children and young people who use services must be

- Fully informed of their care, treatment and support.
- Able to take part in decision making to the fullest extent that is possible.
- Asked if they agree for their parents or guardians to be involved in decisions they need to make.

(Outcome 4I *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010)

Key Service Outcomes

Evidence is increasing that implementation of the national *Quality Criteria for Young People Friendly Services* (Department of Health, London 2011) have the potential to greatly improve patient experience, leading to better health outcomes for young

people and increasing socially responsible life-long use of the NHS. Implementation is also expected to contribute to improvements in health inequalities and public health outcomes e.g. reduced teenage pregnancy and STIs, and increased smoking cessation. All providers delivering services to young people should be implementing the good practice guidance which delivers compliance with the quality criteria.

Poorly planned transition from young people's to adult-oriented health services can be associated with increased risk of non adherence to treatment and loss to follow-up, which can have serious consequences. There are measurable adverse consequences in terms of morbidity and mortality as well as in social and educational outcomes. When children and young people who use paediatric services are moving to access adult services (for example, during transition for those with long term conditions), these should be organised so that:

- All those involved in the care, treatment and support cooperate with the planning and provision to ensure that the services provided continue to be appropriate to the age and needs of the person who uses services.

The *National Minimum Standards for Providers of Independent Healthcare*, (Department of Health, London 2002) require the following standards:

- **A16.1** Children are seen in a separate out-patient area, or where the hospital does not have a separate outpatient area for children, they are seen promptly.
- **A16.3** Toys and/or books suitable to the child's age are provided.
- **A16.8** There are segregated areas for the reception of children and adolescents into theatre and for recovery, to screen the children and adolescents from adult
- Patients; the segregated areas contain all necessary equipment for the care of children.
- **A16.9** A parent is to be actively encouraged to stay at all times, with accommodation made available for the adult in the child's room or close by.
- **A16.10** The child's family is allowed to visit him/her at any time of the day, except where safeguarding procedures do not allow this
- **A16.13** When a child is in hospital for more than five days, play is managed and supervised by a qualified Hospital Play Specialist.
- **A16.14** Children are required to receive education when in hospital for more than five days; the Local Education Authority has an obligation to meet this need and are contacted if necessary.
- **A18.10** There are written procedures for the assessment of pain in children and the provision of appropriate control.

All hospital settings should meet the *Standards for the Care of Critically Ill Children* (Paediatric Intensive Care Society, London 2010).

There should be age specific arrangements for meeting Regulation 14 of the Health and Social Care Act 2008 (Regulated Activities) Regulations 2010. These require:

- A choice of suitable and nutritious food and hydration, in sufficient quantities to meet service users' needs;
- Food and hydration that meet any reasonable requirements arising from a service user's religious or cultural background

- Support, where necessary, for the purposes of enabling service users to eat and drink sufficient amounts for their needs.
- For the purposes of this regulation, "food and hydration" includes, where applicable, parenteral nutrition and the administration of dietary supplements where prescribed.
- Providers must have access to facilities for infant feeding, including facilities to support breastfeeding (Outcome 5E, of the Essential Standards of Quality and Safety, Care Quality Commission, London 2010)

All paediatric patients should have access to appropriately trained paediatric trained dieticians, physiotherapists, occupational therapists, speech and language therapy, psychology, social work and CAMHS services within nationally defined access standards.

All children and young people should have access to a professional who can undertake an assessment using the Common Assessment Framework and access support from social care, housing, education and other agencies as appropriate

All registered providers must ensure safe use and management of medicines, by means of the making of appropriate arrangements for the obtaining, recording, handling, using, safe keeping, dispensing, safe administration and disposal of medicines (Outcome 9 *Essential Standards of Quality and Safety*, Care Quality Commission, London 2010). For children, these should include specific arrangements that:

- Ensures the medicines given are appropriate and person-centred by taking account of their age, weight and any learning disability.
- Ensuring that staff handling medicines have the competency and skills needed for children and young people's medicines management.
- Ensures that wherever possible, age specific information is available for people about the medicines they are taking, including the risks, including information about the use of unlicensed medicine in paediatrics.

Many children with long term illnesses have a learning or physical disability. Providers should ensure that:

- They are supported to have a health action plan
- Facilities meet the appropriate requirements of the Disability Discrimination Act 1995
- They meet the standards set out in Transition: getting it right for young people. Improving the transition of young people with long-term conditions from children's to adult health services. Department of Health Publications, 2006, London

Appendix VII - Payment by Results guidance 2013-14

Taken from –

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf (accessed 14.10.13).

Cystic fibrosis

704. We are introducing a year-of-care tariff for patients with cystic fibrosis (CF) by transitioning from non-mandatory to mandatory prices.

Currency

705. The CF currency is a complexity-adjusted yearly banding system with seven bands of increasing complexity. There is no distinction between adults and children.

Banding

706. Bandings are derived from clinical information including cystic fibrosis complications and drug requirements. The bands range from band one, for the patients with the mildest care requirements (involving outpatient treatment two to three times a year and oral medication) to band five, for patients at the end stage of their illness (requiring intravenous antibiotics in excess of 113 days a year with optimum home or hospital support).

707. The CF tariff is designed to allow specialist CF multidisciplinary teams to direct care in a seamless, patient centred manner, removing any perverse incentives to hospitalise patients who can be well managed in the community and in their home. Furthermore, it will allow early intervention, as per international guidelines, to prevent disease

Gateway ref. 18768 139

progression for example through the use of anti-pseudomonas, inhaled/nebulised antibiotics and mucolytic therapy.

708. Patients are allocated to a band by the Cystic Fibrosis Trust using data from its national database, the UK CF Registry, and feeding it into a template that produces the banding.

709. Banding will be issued each February using the data input to the UK CF Registry. This information is based on a calendar year's data and will be used both to fine tune the planning assumptions made for the next financial year and for initial planning purposes for the following year. Access to the banding data from the registry and information on the number of patients being cared for must be made by the lead clinician in each trust.

710. The bands issued in February 2013 by the CF Registry will be the final bands for all patients for 2013-14 and will be used for contracting purposes. There will be no movement of patients between bands during any one financial year as a full year of data is required for a patient to be appropriately banded.

711. Each provider will be responsible for ensuring that there is sufficient quality data for a patient to be banded through the CF Registry.

Patient numbers

712. Each year there are likely to be changes in the number of patients in each band in the cohort of CF patients at any one centre. This may be due to increases and decreases in patient numbers due to births, transition from children's to adult services, natural patient movement from one area to another, transplantation and deaths. Whilst the tariff is payment for a year of care, in reality payments are most likely to be made in twelfths as part of contract payments. Changes in patient numbers will be addressed as follows:

    (a) New births.
    Payment is calculated from the beginning of the month in which the patient is born. New births will be banded as 2A, which recognises the additional costs associated with diagnosis, care and treatment of a new patient. These patients will move to the band derived from the matrix process described above when the bandings are revised for the following year.

    (b) Transition to adult services or another specialist CF centre.
    Clinical transition or transfer to another centre may take place at any time during the year. **For the purposes of payment** the two centres must agree a date at which responsibility of care will transfer. The date on which responsibility ceases must always be the last day of a calendar month and the date on which the new centre assumes responsibility for care must always be the first day

of the new calendar month. These finalised dates will be used by commissioners to cease payment to the original centre and commence payment to the receiving centre.

In some circumstances, such as where young people are away at university or patients need care whilst on holiday, there may not be a formal transfer of care, as an individual may not wish or need to have their care transferred to a new centre. Should treatment be required when someone is away from the centre responsible for their care, the hospital should submit reasonable costs to the responsible centre for the cost of the treatment provided and the responsible centre will be expected to pay for that care. This will be a provider to provider transaction.

(c) Deaths. Payments for patients who die will cease at the end of the month in which they die.

(d) Transplants. Heart and heart/lung, lung and other transplants have a separate commissioning mechanism. Payment of the CF tariff for patients receiving a transplant will cease at the end of the month in which they receive their transplant. Commissioning of any continuing care from a CF specialist centre following a transplant will be part of the transplant commissioning arrangements.

Information on patient number variations

713. Each provider will be responsible for informing commissioners of changes in patient numbers due to new births, newly diagnosed patients, transition and transfers, deaths and transplants to enable commissioners to reconcile payments on a regular basis. The UK CF Registry will be used to verify the changes reported by providers and ongoing validation of patient numbers will be undertaken through the CF Trust.

714. It will be incumbent upon providers to agree upon payment for any patient who has not formally transferred responsibility for their care to another centre.

715. Some patients may express a desire not to be registered with the CF Trust. If this is the case the provider will need to work with the CF Trust to discuss how the appropriate band can be established.

What is included in the tariffs?

716. The tariffs cover all treatment **directly related to cystic fibrosis** for a patient during the financial year. This includes:

(a) Admitted patient care and outpatient attendances (whether delivered in a specialist centre or under shared network care arrangements)

(b) Home care support, including home intravenous antibiotics supervised by the CF service, home visits by the multidisciplinary team to monitor a patient's condition, eg management of totally implantable venous access devices (TIVADs), collection of mid-course aminoglycoside blood levels and general support for patient and carers
(c) Intravenous antibiotics provided during in-patient spells
(d) Annual review investigations.

717. Any episode directly related to CF specific care (admitted patient care or outpatient activity) will not attract additional activity based payments as these are included in the annual banded tariff, eg admitted for treatment of exacerbation of chest infection, admitted for medical treatment of CF distal intestinal obstruction syndrome, admitted with a new diagnosis of CF-related diabetes to establish a new insulin regimen.

718. For any patient admission or outpatient contact that is for the purpose of cystic fibrosis, the HRG is included in the Year of Care tariff regardless of whether it is one of the CF specific diagnosis driven HRGs or not. We would expect all outpatient CF activity is recorded against TFC 264 and TFC 343.

719. Some elements of services, included in the CF tariffs, may be provided by community services and not the specialist CF centre, such as home care support, including home intravenous antibiotics supervised by the cystic fibrosis service, home visits by the multidisciplinary team to monitor a patient's condition (eg management of totally implantable venous access devices (TIVADs)) and collection of mid-course aminoglycoside blood levels. In such cases there will need to be agreement between the relevant parties on reimbursement from the tariffs paid to the specialist CF centre.

What is excluded from the tariffs?

720. The following are excluded from the mandatory CF tariff:

(a) High cost CF specific **inhaled/nebulised** drugs: Colistimethate sodium, Tobramycin, Dornase alfa, Aztreonam Lysine, Ivacaftor and Mannitol.
(b) Insertion of gastrostomy devices (PEG) and insertion of totally implantable venous access devices (TIVADs) are not included in the annual banded tariff. These surgical procedures should be reimbursed via the relevant HRG tariff.
(c) Neonates admitted with meconium ileus who are subsequently identified to have cystic fibrosis should not be subject to the CF tariff until they have been discharged after their initial surgical procedure. This surgical procedure should be reimbursed via the relevant HRG tariff. Once discharged after their initial surgical procedure subsequent CF treatment will be covered by the CF

tariff. Annual banding should not include the period they spent as an admitted patient receiving their initial surgical management.

721. CF patients may require medical input from other specialties for non-CF specific care. The costs relating to non-CF specific care are not included in the annual banded tariff. These episodes of care will be covered by tariffs assigned to the relevant HRG or TFC, eg obstetric care for a female patient with CF, activity associated with CF related diabetes, ENT outpatient review for nasal polyps and ENT surgery for removal of nasal polyps.

Drugs

722. Prescription of the high cost drugs Colistimethate sodium, Tobramycin, Dornase alfa, Ivacaftor and Aztreonam Lysine that are used in the treatment of CF patients will be initiated by the specialist CF centre. Continuation of the prescription, whether from the specialist CF centre or the GP, will be by local arrangement.

723. Funding of Colistimethate sodium, Tobramycin, Dornase alfa, Ivacaftor and Aztreonam Lysine will be governed by the national commissioning policy. Commissioners will need to ensure that the arrangements are clear with each specialist CF centre for the continuing prescription of these drugs to enable the appropriate funding flow.

724. Where continuation of prescribing is left with the specialist CF centre, the use of home delivery systems should be encouraged.

725. GPs will continue to prescribe and fund all other chronic specific medication, for example long-term oral antibiotics, pancreatic enzyme replacement therapy and vitamin supplements.

726. There is a number of high cost antifungal treatments excluded from PbR, which are therefore not included in the CF tariff.

727. Costs associated with long-term nutritional supplementation via gastrostomy or nasogastric tube feeding are not included in the CF tariff.

728. Commissioning of nutritional supplements will continue to be the responsibility of CCGs. However there must be close liaison between the specialist CF centre and Primary Care to ensure the continued prescription of the most appropriate supplement.

Tariff principles

729. CF care is provided on the basis of the following principles:

(a) All patients will be registered with a CF specialist centre which will be responsible for all care directly related to the patient's CF.

(b) CF centres will be responsible for ensuring that the data for all the patients for whom they are responsible are entered on the national CF database, the UK CF Registry. If patients/carers do not wish to have their data to be entered on the UK CF Registry, they must express this wish in writing to their clinician at the specialist centre and the centre will need to work with the CF Trust to establish an appropriate band.
(c) All CF treatment and care for both adults and children will be delivered by clearly designated providers.
(d) For adults all the treatment and care will be the responsibility of the specialist centre with no shared care arrangements in place.
(e) For children, the treatment centre will initiate all treatments with treatment and care being delivered in either a centre or designated district general hospitals within the framework of network care. Inter-trust service level agreements will be in place to support these arrangements.
(f) The providers of CF services – centres and network units – will need to comply with the relevant service specification and meet the service standards.
(g) Access to and eligibility for CF specialist drugs will be determined by national commissioning policy.
(h) The relevant CF centre will be responsible for initiating all current CF specialist drugs.

730. Using these principles, payment of CF tariffs will only be made to specialised CF centres from whom the NHS Commissioning Board is commissioning CF services. The formal process of designating treatment centres will take some time and further guidance will be issued through the NHS Commissioning Board.

Network/Outreach care

731. Network care is a recognised model for paediatric care. Network care clinics take place in district general hospitals close to the homes of people with CF, where care is provided in partnership with the responsible specialist CF centre. This model must provide care that is of equal quality and access as full specialist centre care.

732. Discussions regarding network care arrangements have identified the need to clearly define the responsibilities of specialist centres and their relationship with shared care providers. A full description of responsibilities of the CF specialist centre in the paediatric network model of care is included in the national service specification.

733. Outreach care is defined as care provided by a specialist centre care team who travel to a local district general hospital. In all cases, CF tariffs will only be paid to designated specialist CF centres.

Payment for Network care

734. Payment of tariffs will only be made to specialist centres which may then elect to undertake network care with shared care providers. There will need to be an agreement of the appropriate reimbursement between the specialist provider and each appropriate network provider based on delivered inputs and compliance with the relevant service specification and service standards.

Details of the tariffs

735. The tariffs for 2013-14 are included in the *tariff information spreadsheet*. The tariffs for bands 1A and 2 remain the same, reflecting the similar costs of service provision. As cystic fibrosis is in itself a specialised service the tariffs are not eligible for any top-up.

Appendix VII - Guide for parents starting a child on a nebulised therapy

Royal Brompton & Harefield NHS
NHS Foundation Trust

Pseudomonas, Antibiotics and Nebulisers.....a guide for parents and carers

This guide is designed for parents and carers whose child is starting nebulised antibiotics for the first time. It is intended to be read before your child starts antibiotic nebulisers. It is likely that these antibiotics will be required twice a day for at least 3 months so introducing them carefully is essential. We hope that this guide will help you and your child over the next few weeks.

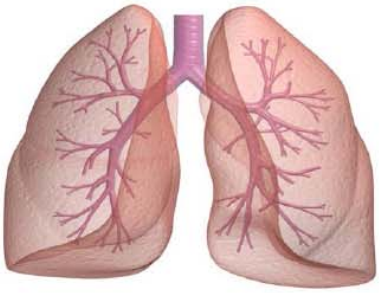
At the back of this guide is a notes page for you to record useful information or any questions you may have for the team.

Pseudomonas...

What is it? Pseudomonas aeruginosa to give it its full name (or P aeruginosa or PsA) is a bacterium that is often found in damp soil and stagnant water. As it is found in so many places it would be virtually impossible to prevent a child coming into contact with it at some point in their lives.

If your child's cough swab or sputum sample grows Pseudomonas the first treatment might be a course of oral antibiotics (Ciprofloxacin) as well as nebulised antibiotics (Colistin) i.e antibiotics in a mist that your child breathes in.

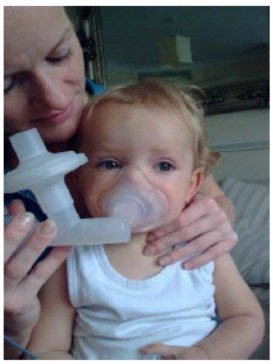
Nebulised Antibiotics...



Breathing in a mist of antibiotic medicine allows it to get directly to the lungs. The fine mist allows the smaller particles of medicine to get to the hard to reach parts of the lungs. A nebuliser also allows a higher dose of medicine to be given safely.

Nebulisers work best when your child is relaxed and breathing normally. We will give you some tips and ideas to get your child used to the nebuliser and the mask further on in this leaflet. Wherever possible we will give you a faster quieter nebuliser such as a Pari eFlow©

Taking the nebuliser for the first time



In order to make sure that your child doesn't get wheezy when he/she has the nebulised antibiotics for the first time, we give the first dose at the Brompton.

On the day of the first dose (the trial) your child will be seen as an Outpatient and they will be monitored whilst they have their first dose of nebulised antibiotic. For older children they will have a lung function test before and afterwards. Younger children will have their oxygen levels monitored with a pulse oximeter (as they would in clinic) and the physio will listen to their chest. Consider bringing treats for younger children as well as a favourite toy and DVD.

Getting used to the nebuliser .....a staged approach

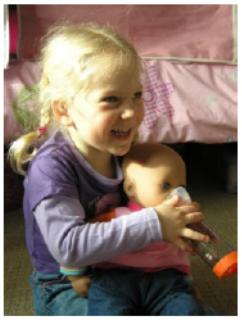
Once the Outpatient department has been notified that your child is starting nebulisers they will post a mask, filter and mouthpiece to you depending on the age of your child. You will receive the nebuliser itself when you visit the Physiotherapy department.

When you have received your mask, mouthpiece or other equipment try the following.....

Stage 1 Play with the mask on a doll / toy, parents / carers. Once happy playing you can then put the mask to your child's face. Don't forget you can play with the mask at bath time as well

After the trial and you have the nebuliser at home.....

Stage 2 Look at the nebuliser together and play with the parts. Turn it on and play with it for no more than five minutes. (Don't put any antibiotic medicine in at this stage)



Stage 3 Choose a DVD to watch and 'nebulise' a doll, teddy or favourite toy

Stage 4 Using the same DVD fully assemble the nebuliser and play with the mask on your child's face. Start with 10 seconds and build up. Give lots of encouragement and rewards such as stickers or sweets if appropriate.

Stage 5 As above but use some of the **0.9% saline** in the nebuliser. Use a timer and see if your child can manage 30 seconds 3-4 times in a row. If so move onto the next stage.

Stage 6 Your child should be ready to take the nebulised antibiotic. Keep giving lots of encouragement and praise. Your child might find it helpful to have a 5 minute warning before you start. Use the same DVD and then switch it off afterwards ready for the next time.

Remember, we want you and your child to be as comfortable and relaxed as possible so that the antibiotics can work really well. If your child is under 5 the homecare physiotherapists will ring you during this time but please contact the team if you feel you need extra support.

Top Tips from other parents

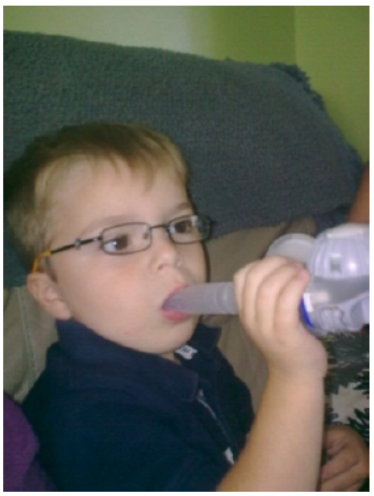
Best time Think about when you can best fit the nebuliser into your everyday routine. Remember the antibiotic should be after physiotherapy. Try and pick a time when you will not be interrupted and are generally relaxed without time pressure

Discussion Is your child old enough to be prepared verbally eg "The doctors have asked you to take a new medicine to help with your cough. It is a special mist which you have to breathe in. You do it twice a day like cleaning your teeth."

Consistency Have a consistent approach. Same time, same place, same DVD etc.

Rewards With younger children (pre-school to 7 year olds) it can be really helpful to have prepared small immediate treats such as a sticker or sweet. What other younger (and older) patients seem to love is having a special jar/pot/bag used only to reward co-operation with the nebuliser. This can either be full of small treats (chocolate buttons/stickers/other items such as Moshi Monsters or Match Attack cards.) Alternatively it could be a lucky dip of instant privileges - for example watching Peppa Pig or reading a book with Mum/Dad. Older children may like the lucky dip approach or can be offered more planned rewards if preferred, such as staying up later or having a friend to play.

Keep Calm Keeping calm yourself will help your child to learn quickly to get used to using the nebuliser. Even if underneath you do not feel calm (we do understand that your child being prescribed nebulised antibiotics may be difficult for you for a number of reasons) try to 'act 'calm. Think about your movements, tone of voice and what you are saying.



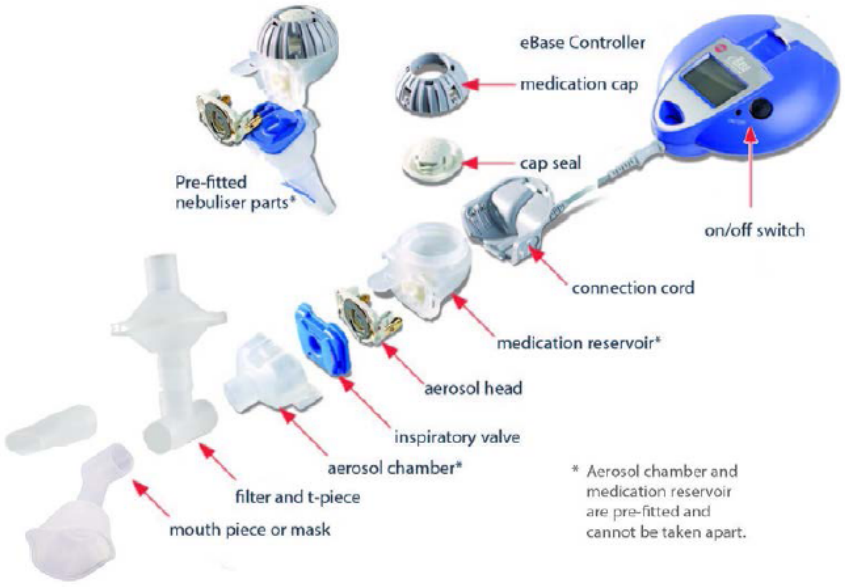
Get ready Take time to get used to the equipment. Make sure you have everything ready before you start. At the beginning your child may be worried that you are using a needle to mix up the medicine so this is best done out of sight. Give a 5 minute warning.

Distraction Have other means of distraction handy as well as a DVD e.g. books and toys. You will need to bring these with you to the trial appointment as well.

When things go wrong If at any time during the 'stages' your child becomes distressed, remove the nebuliser without comment. It is important not to 'reward' the child by giving them a cuddle, or getting cross with them. Just walk calmly away and say ' that's ok, we will try again next time'. You may find it helpful to go back a stage. Please contact one of the people on the Useful Contacts list below to discuss further.

How to put the eFlow together

To familiarise yourself with the nebuliser you may find it helpful to look at the Pari website before your visit: www.parimedical.co.uk/consumer_information/video_center.html



"At the beginning it looked really complicated but I soon got the hang of it. I don't even think about it now" **(Mum of a 2yr old boy)**

How to make up the Colomycin…

Colomycin comes in a dry powder. You will have to dissolve it using 0.9% saline (salty water). Your physio will give you full written instructions for mixing Colomycin specific to your child's prescription.

To familiarise yourself with the Colomycin medicine you may find it helpful to look at the 4 minute Youtube video "Colomycin Educational Patient Guide – Instructions for nebulisation" - www.youtube.com/watch?v=U6RsaKmQcTU

FAQs...

Can I give the nebuliser to my child when they are asleep?

There needs to be exceptional circumstances when this may work best but there are reasons why it may not be the most helpful thing to do. Please do not do it because your child becomes distressed when they have the nebuliser while awake - their fears are likely to be heightened by being woken by the nebuliser. If this is the only way you are able to ensure that your child co-operates with the nebuliser, please do contact one of the people on the Useful Contacts list below for some suggestions about how to help with this.

There seems to be some medicine left in the nebuliser when it's finished – is this right?

There will always be some medicine left over as the nebuliser is more efficient.

How do I wash the equipment?

Keeping your nebuliser clean is vitally important. Full details will be given by your physiotherapist at the trial. Full washing instructions for the Pari eFlow nebuliser can be found here: www.parimedical.co.uk/products/lower_airways/product/detail/info/videos/eflow_rapid_nebuliser_system-1.htm

If despite following all these guidelines your child is finding the nebuliser difficult please let your homecare team know and we will work with you to make it successful.

Useful Contacts...

Homecare Physiotherapists	Emma Dixon	07970 269452
	Nicky Murray	07791 584749
Homecare nursing team	Pat Stringer	07973 173969
	Karen Henney	07971 224068
Ward Physiotherapists	Nic Collins	0207 352 8121 Bleep 7304
Paediatric Clinical Psychology		020 7351 8251

Notes...

Check List for the Trial...

Don't forget to bring

- **ALL the equipment that you have been sent e.g. mask, filter, mouthpiece**
- **Your child's favourite DVD**
- **Your child's favourite doll, teddy or toy**
- **Stickers, sweets or other "rewards"**
- **A list of any questions you may have**

This leaflet was produced by the Physiotherapy Dept.

Royal Brompton & Harefield NHS
NHS Foundation Trust

Appendix IX –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 X – Travel letters

Date:

TO WHOM IT MAY CONCERN

Dear Sir/Madam,

Re:

The above mentioned child has cystic fibrosis and is currently under our 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 the department at the Royal Brompton Hospital on 0207-351 8755.

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.

If any further information is required, please do not hesitate to contact the department at the Royal Brompton Hospital on 0207-351 8755.

Yours faithfully,

PRINT NAME:

Signed:

Appendix XI – Gene mutation nomenclature

http://www.umd.be/CFTR/W_CFTR/CFTR_variation.pdf

cDNA Reference sequence **NM_000492.3 with the exception of c.1408A instead of G*

***Protein Reference sequence **NP_000483.3** with the exception of p.Met470 instead of p.Val470*

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
prom (1)	48C/G	c.1-85C>G	p.Met1?
prom (1)	125G/C	c.1-8G>C	p.Met1?
E1 (1)	M1V	c.1A>G	p.Met1?
E1 (1)	M1K	c.2T>A	p.Met1?
E1 (1)	M1I(ATA)	c.3G>A	p.Met1?
E1 (1)	S4X	c.11C>A	p.Ser4X
E1 (1)	P5L	c.14C>T	p.Pro5Leu
E1 (1)		c.49_50dup	p.Trp19AlafsX7
E2 (2)	CFTRdele2 ; CFTR- dele2	c.54_164del	p.Ser18_Glu54del
E2-3 (2-3)	CFTRdele2, 3 ; Del exon 2- 3	c.54_273del	p.Ser18ArgfsX16
E2 (2)		c.95T>C	p.Leu32Pro
E2 (2)	S50P	c.148T>C	p.Ser50Pro
IVS1 (1)	185+ 4A- >T	c.53+4A>T	
IVS2 (2)		c.165-2A>C	
IVS2 (2)	297- 3C- >T	c.165-3C>T	
E3 (3)	300delA	c.168delA	p.Glu56AspfsX35
E3 (3)	W57G	c.169T>G	p.Trp57Gly
E3 (3)	D58G	c.173A>G	p.Asp58Gly
E3 (3)	306insA	c.175dup	p.Arg59LysfsX10
E3 (3)	E60K	c.178G>A	p.Glu60Lys
E3 (3)	E60X	c.178G>T	p.Glu60X
E3 (3)	P67L	c.200C>T	p.Pro67Leu
E3 (3)	R74W	c.220C>T	p.Arg74Trp
E3 (3)	R75X	c.223C>T	p.Arg75X
E3 (3)	R75Q	c.224G>A	p.Arg75Gln
E3 (3)		c.228T>G	p.Cys76Trp
E3 (3)	359insT	c.233dup	p.Trp79LeufsX32
E3 (3)	G85E	c.254G>A	p.Gly85Glu
E3 (3)	F87L	c.259T>C	p.Phe87Leu
E3 (3)	394delTT	c.262_263delTT	p.Leu88IlefsX22
IVS3 (3)	405+ 46G/T	c.273+46T>G	
IVS3 (3)	406- 1G- >C	c.274-1G>C	
E4 (4)	Q98R	c.293A>G	p.Gln98Arg
E4 (4)	I105N	c.314T>A	p.Ile105Asn
E4 (4)	D110E	c.330C>A	p.Asp110Glu
E4 (4)	P111L	c.332C>T	p.Pro111Leu

cDNA Reference sequence **NM_000492.3 with the exception of c.1408A instead of G*

***Protein Reference sequence **NP_000483.3** with the exception of p.Met470 instead of p.Val470*

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E4 (4)	R117C	c.349C>T	p.Arg117Cys
E4 (4)	R117H	c.350G>A	p.Arg117His
E4 (4)	Y122X	c.366T>A	p.Tyr122X
E4 (4)	A141D	c.422C>A	p.Ala141Asp
E4 (4)	574delA	c.442delA	p.Ile148LeufsX5
E4 (4)	I148T	c.443T>C	p.Ile148Thr
E4 (4)	M152V	c.454A>G	p.Met152Val
E4 (4)	Y161N	c.481T>A	p.Tyr161Asn
IVS4 (4)	621+ 1G- >T	c.489+1G>T	
IVS4 (4)	621+ 2T- >G	c.489+2T>G	
IVS4 (4)	621+ 3A- >G	c.489+3A>G	
E5 (5)	L165S	c.494T>C	p.Leu165Ser
E5 (5)	R170H	c.509G>A	p.Arg170His
E5 (5)	I175V	c.523A>G	p.Ile175Val
E5 (5)	G178R	c.532G>A	p.Gly178Arg
E5 (5)	N186K	c.558C>A	p.Asn186Lys
IVS5 (5)	711+ 1G- >T	c.579+1G>T	
IVS5 (5)	711+ 3A- >G	c.579+3A>G	
IVS5 (5)	712- 1G- >T	c.580-1G>T	
E6 (6a)	G194V	c.581G>T	p.Gly194Val
E6 (6a)	F200I	c.598T>A	p.Phe200Ile
E6 (6a)	V201M	c.601G>A	p.Val201Met
E6 (6a)	733delG	c.601delG	p.Val201CysfsX14
E6 (6a)	I203M	c.609C>G	p.Ile203Met
E6 (6a)	L206W	c.617T>G	p.Leu206Trp
E6 (6a)	Q220X	c.658C>T	p.Gln220X
E6 (6a)	L227R	c.680T>G	p.Leu227Arg
E6 (6a)	V232D	c.695T>A	p.Val232Asp
E6 (6a)	Q237E	c.709C>G	p.Gln237Glu
E6 (6a)	852del22	c.720_741del	p.Gly241GlufsX13
E6 (6a)	M244K	c.731T>A	p.Met244Lys
IVS6 (6a)	875+ 40A/G	c.743+40A>G	
IVS6 (6a)		c.744-33GATT[4]	
IVS6 (6a)	TTGA repeats	c.744-33GATT[6]	
IVS6 (6a)	TTGA repeats	c.744-33GATT[7]	
IVS6 (6a)	TTGA repeats	c.744-33GATT[8]	

cDNA Reference sequence **NM_000492.3 with the exception of c.1408A instead of G*

***Protein Reference sequence **NP_000483.3** with the exception of p.Met470 instead of p.Val470*

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E7 (6b)	R258G	c.772A>G	p.Arg258Gly
E7 (6b)	N287Y	c.859A>T	p.Asn287Tyr
E7 (6b)	991del5	c.861_865delCTTAA	p.Asn287LysfsX19
IVS7 (6b)		c.869+5G>A	
IVS7 (6b)	1001+ 11C/T	c.869+11C>T	
E8 (7)	1078delT	c.948delT	p.Phe316LeufsX12
E8 (7)	R334W	c.1000C>T	p.Arg334Trp
E8 (7)	I336K	c.1007T>A	p.Ile336Lys
E8 (7)	T338I	c.1013C>T	p.Thr338Ile
E8 (7)	R347P	c.1040G>C	p.Arg347Pro
E8 (7)	R347H	c.1040G>A	p.Arg347His
E8 (7)	R352Q	c.1055G>A	p.Arg352Gln
E8 (7)	1215delG	c.1083delG	p.Trp361CysfsX8
IVS8 (7)	1248+ 1G- >A	c.1116+1G>A	
E9 (8)	E379K	c.1135G>A	p.Glu379Lys
IVS9 (8)	1341+ 18A- >C	c.1209+18A>C	
IVS9 (8)		c.1210-12T[3]	
IVS9 (8)	poly- T tract variations	c.1210-12T[5]	
IVS9 (8)		c.1210-12T[6]	
IVS9 (8)	poly- T tract variations	c.1210-12T[7]	
IVS9 (8)	poly- T tract variations	c.1210-12T[9]	
IVS9 (8)	1342- 12(GT)n	c.1210-34TG[9]	
IVS9 (8)	1342- 12(GT)n	c.1210-34TG[10]	
IVS9 (8)	1342- 12(GT)n	c.1210-34TG[11]	
IVS9 (8)	1342- 12(GT)n	c.1210-34TG[12]	
IVS9 (8)		c.1210-34TG[13]	
E10 (9)	D443Y	c.1327G>T	p.Asp443Tyr
E10 (9)	Q452P	c.1355A>C	p.Gln452Pro
E10 (9)	A455E	c.1364C>A	p.Ala455Glu
IVS10 (9)		c.1392+52T[10]	
IVS10 (9)	1525- 61A/G	c.1393-61A>G	
E11 (10)	1531C/T (L467F)	c.1399C>T	p.Leu467Phe
E11 (10)	M470V	c.1408A>G	p.Met470Val
E11 (10)	1548delG	c.1418delG	p.Gly473GlufsX54
E11 (10)	S489X	c.1466C>A	p.Ser489X
E11 (10)	Q493X	c.1477C>T	p.Gln493X

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***Protein Reference sequence **NP_000483.3** with the exception of p.Met470 instead of p.Val470*

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E11 (10)	1609delCA	c.1477_1478delCA	p.Gln493ValfsX10
E11 (10)	T501A	c.1501A>G	p.Thr501Ala
E11 (10)	I506V (1648A/G)	c.1516A>G	p.Ile506Val
E11 (10)	I506T	c.1517T>C	p.Ile506Thr
E11 (10)	[delta]I507	c.1519_1521delATC	p.Ile507del
E11 (10)	[delta]F508	c.1521_1523delCTT	p.Phe508del
E11 (10)	F508C	c.1523T>G	p.Phe508Cys
E11 (10)	1677delTA	c.1545_1546delTA	p.Tyr515X
E11 (10)	1706del17	c.1574_1590del	p.Gln525LeufsX37
E11 (10)	1716G/A	c.1584G>A	p.Glu528Glu
IVS11 (10)	1716+ 2T- >C	c.1584+2T>C	
IVS11 (10)	1717- 8G- >A	c.1585-8G>A	
IVS11 (10)	1717- 1G- >A	c.1585-1G>A	
E12 (11)	G542X	c.1624G>T	p.Gly542X
E12 (11)	G544V	c.1631G>T	p.Gly544Val
E12 (11)	S549R(T- >G)	c.1647T>G	p.Ser549Arg
E12 (11)	G551D	c.1652G>A	p.Gly551Asp
E12 (11)	R553X	c.1657C>T	p.Arg553X
E12 (11)	1802delC	c.1670delC	p.Ser557PhefsX2
E12 (11)	L558S	c.1673T>C	p.Leu558Ser
E12 (11)	R560K	c.1679G>A	p.Arg560Lys
IVS12 (11)	1811+ 1.6kbA- >G	c.1680-886A>G	
IVS12 (11)	1811 + 1650 T>A	c.1680-870T>A	
IVS12 (11)	1812- 1G- >A	c.1680-1G>A	
E13 (12)	V562I	c.1684G>A	p.Val562Ile
E13 (12)	G576A	c.1727G>C	p.Gly576Ala
E13 (12)	T582I	c.1745C>T	p.Thr582Ile
E13 (12)	E585X	c.1753G>T	p.Glu585X
IVS13 (12)	1898+ 1G- >A	c.1766+1G>A	
IVS13 (12)	1898+ 1G- >C	c.1766+1G>C	
IVS13 (12)	1898+ 5G- >A	c.1766+5G>A	
IVS13 (12)	1898+ 152T/A	c.1766+152T>A	
E14 (13)	I601F	c.1801A>T	p.Ile601Phe
E14 (13)	1949del84	c.1820_1903del	p.Met607_Gln634del
E14 (13)	H609L	c.1826A>T	p.His609Leu
E14 (13)		c.1920T>C	p.Phe640Phe

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Protein Reference sequence **NP_000483.3 with the exception of p.Met470 instead of p.Val470

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E14 (13)	E656X	c.1966G>T	p.Glu656X
E14 (13)	2118del4	c.1986_1989delAACT	p.Thr663ArgfsX8
E14 (13)	E664X	c.1990G>T	p.Glu664X
E14 (13)	R668C	c.2002C>T	p.Arg668Cys
E14 (13)	2143delT	c.2012delT	p.Leu671X
E14 (13)	2183AA- >G	c.2051_2052delinsG	p.Lys684SerfsX38
E14 (13)	2183delAA	c.2051_2052delAA	p.Lys684ThrfsX4
E14 (13)	2184insA	c.2052dup	p.Gln685ThrfsX4
E14 (13)	R709X	c.2125C>T	p.Arg709X
E14 (13)	K710X	c.2128A>T	p.Lys710X
E14 (13)	E725K	c.2173G>A	p.Glu725Lys
E14 (13)	L732X	c.2195T>G	p.Leu732X
E14 (13)	S737F	c.2210C>T	p.Ser737Phe
E14 (13)	2377C/T	c.2245C>T	p.Leu749Leu
E14 (13)	2380_2387del	c.2248_2255del	p.Pro750GlnfsX26
E14 (13)	2391 C/T	c.2259C>T	p.Ser753Ser
E14 (13)	R764X	c.2290C>T	p.Arg764X
E14 (13)	2423delG	c.2291delG	p.Arg764GlnfsX7
E14 (13)	2456delAC	c.2324_2325delAC	p.His775LeufsX3
E14 (13)	S776X	c.2327C>G	p.Ser776X
E14 (13)	R792X	c.2374C>T	p.Arg792X
E14 (13)	K830X	c.2488A>T	p.Lys830X
IVS14 (13)	2622+ 1G- >A	c.2490+1G>A	
E15 (14a)		c.2496C>A	p.Cys832X
E15 (14a)	2634delT	c.2502delT	p.Phe834LeufsX10
E15 (14a)	2634insT	c.2502dup	p.Asp835X
E15 (14a)	2640delT	c.2508delT	p.Asp836GlufsX8
E15 (14a)	W846X (2670TGG>TGA)	c.2538G>A	p.Trp846X
E15 (14a)	R851X	c.2551C>T	p.Arg851X
E15 (14a)	2694T/G	c.2562T>G	p.Thr854Thr
E15 (14a)	2711delT	c.2583delT	p.Phe861LeufsX3
E15 (14a)	C866R	c.2596T>C	p.Cys866Arg
IVS15 (14a)		c.2620-17G>T	
IVS16 (14b)	2789+ 5G- >A	c.2657+5G>A	
IVS16 (14b)	2790- 1G- >C	c.2658-1G>C	
E17 (15)	Q890X	c.2668C>T	p.Gln890X

cDNA Reference sequence **NM_000492.3 with the exception of c.1408A instead of G*

***Protein Reference sequence **NP_000483.3** with the exception of p.Met470 instead of p.Val470*

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E17 (15)	S902R	c.2706C>G	p.Ser902Arg
E17 (15)	2851A/G	c.2719A>G	p.Ile907Val
E17 (15)	2869insG	c.2736dup	p.Tyr913ValfsX62
E17 (15)	2896insAG	c.2763_2764dup	p.Val922GlufsX2
E17 (15)	D924N	c.2770G>A	p.Asp924Asn
E17 (15)	S945L	c.2834C>T	p.Ser945Leu
E17 (15)	M952I	c.2856G>C	p.Met952Ile
E17 (15)	3007delG	c.2875delG	p.Ala959HisfsX9
E17 (15)	3030G/A	c.2898G>A	p.Thr966Thr
E17 (15)	L967S	c.2900T>C	p.Leu967Ser
IVS17 (15)	CFTRdele16- 17b ; CFTR-dele 16- 17a- 17b	c.2909_3367del	p.Gly971_Gly1123del
IVS17 (15)	3041- 15T- >G	c.2909-15T>G	
IVS17 (15)	3041- 92G/A	c.2909-92G>A	
IVS17 (15)	3041- 71G/C	c.2909-71G>C	
E18 (16)	S977F	c.2930C>T	p.Ser977Phe
E18 (16)	I980K	c.2939T>A	p.Ile980Lys
E18 (16)	D985H	c.2953G>C	p.Asp985His
E18 (16)	D993Y	c.2977G>T	p.Asp993Tyr
E18 (16)	F994C	c.2981T>G	p.Phe994Cys
E18 (16)	3120G- >A	c.2988G>A	p.Gln996Gln
IVS18 (16)	3120+ 1G- >A	c.2988+1G>A	
E19 (17a)	L997F	c.2991G>C	p.Leu997Phe
E19 (17a)		c.2989_3139del	p.Leu997AlafsX13
E19 (17a)	3121- 977_3499+ 248del2515	c.2989_3367del	p.Leu997GlufsX11
E19 (17a)	Del exon 17a- 17b	c.2989_3468del	p.Leu997_Leu1156del
IVS18 (16)	3121- 92A12/13	c.2989-93A[12]	
IVS18 (16)	3121- 1G- >A	c.2989-1G>A	
E19 (17a)	3129del4	c.2997_3000delAATT	p.Ile1000X
E19 (17a)	I1005R	c.3014T>G	p.Ile1005Arg
E19 (17a)	3196del54	c.3064_3117del	p.Val1022_Gln1039del
E19 (17a)	3195del6 ; 3199del6	c.3067_3072del	p.Ile1023_Val1024del
E19 (17a)	3200_3204delTAGTG	c.3068_3072delTAGTG	p.Ile1023SerfsX22
E19 (17a)	I1027T	c.3080T>C	p.Ile1027Thr
E19 (17a)	M1028R	c.3083T>G	p.Met1028Arg
E19 (17a)	Y1032C	c.3095A>G	p.Tyr1032Cys

cDNA Reference sequence **NM_000492.3 with the exception of c.1408A instead of G*

***Protein Reference sequence **NP_000483.3** with the exception of p.Met470 instead of p.Val470*

#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E19 (17a)	Q1042X	c.3124C>T	p.Gln1042X
E19 (17a)		c.3131A>G	p.Glu1044Gly
IVS19 (17a)	3271+ 1G- >A	c.3139+1G>A	
IVS19 (17a)	3271+ 18C/T	c.3139+18C>T	
IVS19 (17a)	3272- 93T/C	c.3140-92T>C	
IVS19 (17a)	3272- 26A- >G	c.3140-26A>G	
E20 (17b)	W1063X	c.3189G>A	p.Trp1063X
E20 (17b)	L1065P	c.3194T>C	p.Leu1065Pro
E20 (17b)	R1066C	c.3196C>T	p.Arg1066Cys
E20 (17b)	A1067T	c.3199G>A	p.Ala1067Thr
E20 (17b)	R1070W	c.3208C>T	p.Arg1070Trp
E20 (17b)	F1074L	c.3222T>A	p.Phe1074Leu
E20 (17b)		c.3263dup	p.Asn1088LysfsX68
E20 (17b)	Y1092X(C- >A)	c.3276C>A	p.Tyr1092X
E20 (17b)	3417A/T	c.3285A>T	p.Thr1095Thr
E20 (17b)	R1102X	c.3304A>T	p.Arg1102X
E20 (17b)	E1104X	c.3310G>T	p.Glu1104X
IVS20 (17b)	3499+ 37G/A	c.3367+37G>A	
IVS20 (17b)	3500- 140A/C	c.3368-140A>C	
E21 (18)	3532AC- >GTA	c.3400_3401delinsGTA	p.Thr1134ValfsX22
E21 (18)	D1152H	c.3454G>C	p.Asp1152His
E21 (18)	V1153E	c.3458T>A	p.Val1153Glu
E21 (18)	3600G- >A	c.3468G>A	p.Leu1156Leu
IVS21 (18)	3601- 65C/A	c.3469-65C>A	
E22 (19)	CFTRdele19	c.3469_3717del	p.Met1157_Arg1239del
E22 (19)	R1158X	c.3472C>T	p.Arg1158X
E22 (19)	R1162X	c.3484C>T	p.Arg1162X
E22 (19)	3617G/T	c.3485G>T	p.Arg1162Leu
E22 (19)	D1168G	c.3503A>G	p.Asp1168Gly
E22 (19)	3659delC	c.3528delC	p.Lys1177SerfsX15
E22 (19)	3737delA	c.3605delA	p.Asp1202AlafsX9
E22 (19)	S1206X(C>A)	c.3617C>A	p.Ser1206X
E22 (19)	3750delAG	c.3618_3619delAG	p.Gly1208ProfsX56
E22 (19)	3755delG	c.3623delG	p.Gly1208AlafsX3
E22 (19)	I1234V	c.3700A>G	p.Ile1234Val
E22 (19)	S1235R	c.3705T>G	p.Ser1235Arg

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#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
IVS22 (19)	3849+ 40A- >G	c.3717+40A>G	
IVS22 (19)	3849+ 10kbC- >T	c.3718-2477C>T	
IVS22 (19)	3850- 1G- >A	c.3718-1G>A	
E23 (20)	G1244E	c.3731G>A	p.Gly1244Glu
E23 (20)	G1249E	c.3746G>A	p.Gly1249Glu
E23 (20)	S1251N	c.3752G>A	p.Ser1251Asn
E23 (20)	3905insT	c.3773dup	p.Leu1258PhefsX7
E23 (20)	D1270N	c.3808G>A	p.Asp1270Asn
E23 (20)	W1274X	c.3822G>A	p.Trp1274X
E23 (20)	W1282X	c.3846G>A	p.Trp1282X
E23 (20)	P1290P (4002A/G)	c.3870A>G	p.Pro1290Pro
IVS23 (20)	4005+ 1G- >A	c.3873+1G>A	
IVS23 (20)	4006- 200G/A	c.3874-200G>A	
E24 (21)	4010del4	c.3883_3886delATTT	p.Ile1295PhefsX32
E24 (21)	4015delA	c.3883delA	p.Ile1295PhefsX33
E24 (21)	4016insT	c.3889dup	p.Ser1297PhefsX5
E24 (21)	4029A/G	c.3897A>G	p.Thr1299Thr
E24 (21)	N1303H	c.3907A>C	p.Asn1303His
E24 (21)	N1303K	c.3909C>G	p.Asn1303Lys
E24 (21)	D1305E	c.3915T>A	p.Asp1305Glu
E24 (21)	Q1313X	c.3937C>T	p.Gln1313X
IVS24 (21)		c.3963+69A>G	
IVS24 (21)	4096- 283T/C	c.3964-283T>C	
IVS24 (21)	4096- 3C- >G	c.3964-3C>G	
E25 (22)	CFTRdele22, 23	c.3964_4242del	p.Val1322_Leu1414del
E25 (22)	Del exon 22- 24	c.3964_4440del	p.Val1322_Leu1480del
E25 (22)	G1349D	c.4046G>A	p.Gly1349Asp
E25 (22)	Q1352H(G- >C)	c.4056G>C	p.Gln1352His
E25 (22)	4218insT	c.4086dup	p.Lys1363X
E25 (22)	A1364V	c.4091C>T	p.Ala1364Val
E25 (22)	I1366T	c.4097T>C	p.Ile1366Thr
E25 (22)	D1377H	c.4129G>C	p.Asp1377His
IVS25 (22)	4269- 139G/A	c.4137-139G>A	
E26 (23)	Q1382X	c.4144C>T	p.Gln1382X
E26 (23)	4279insA	c.4147dup	p.Ile1383AsnfsX3
E26 (23)	Q1390X	c.4168C>T	p.Gln1390X

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#exon/intron (#usual)	Usual name (CFMD)	c.DNA nomenclature UMD*	Predicted protein UMD**
E26 (23)	4332delTG	c.4200_4201delTG	p.Cys1400X
IVS26 (23)	4374+ 1G- >A	c.4242+1G>A	
IVS26 (23)	4374+ 13A/G	c.4242+13A>G	
IVS26 (23)	4374_4374+ 1GG>TT	c.4242_4242+1delinsTT	
E27 (24)	4382delA	c.4251delA	p.Glu1418ArgfsX14
E27 (24)	R1422W	c.4264C>T	p.Arg1422Trp
E27 (24)	4404C/T	c.4272C>T	p.Tyr1424Tyr
E27 (24)	S1426P	c.4276T>C	p.Ser1426Pro
E27 (24)	4521G/A	c.4389G>A	p.Gln1463Gln
E27 (24)	Q1476X	c.4426C>T	p.Gln1476X

Appendix XII – CF Trust consensus documents, factsheets & leaflets

These are available on the CF Trust website – https://www.cysticfibrosis.org.uk/about-cf/publications.aspx Can also be accessed via links below if reading this online (CTRL + click on title).

Consensus Documents

Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK. Second edition. December 2011.
Consensus document outlining standards of care.

Pharmacy Standards of Care. November 2011.
Consensus document outlining pharmacy standards in CF care.

Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis. Second edition. June 2011.
Consensus document outlining standards of care and food practice for physiotherapy.

Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis. First edition. September 2010.
Consensus document outlining laboratory standards for processing microbiological samples.

Antibiotic Treatment for Cystic Fibrosis. Third edition. May 2009.
Consensus document on antibiotic treatment for CF.

Methicillin-resistant Staphylococcus aureus (MRSA). April 2008.
Consensus document on MRSA

Bone Mineralisation in Cystic Fibrosis. February 2007. (Not to be downloaded without addendum, below). (PDF 762KB)
Consensus document on bone mineralisation in CF.
Addendum for Bone Mineralisation in Cystic Fibrosis.
Addendum for Bone Mineralisation consensus document.

Pseudomonas aeruginosa infection in people with Cystic Fibrosis. Suggestions for Prevention and Infection Control. Second Edition. November 2004.
Consensus document on prevention and infection control of *Pseudomonas aeruginosa*.

The Burkholderia cepacia Complex - Suggestions for Prevention and Infection Control. Second edition. September 2004.
Consensus document on suggestions for prevention and infection control of Burkholderia cepacia Complex.

Management of Cystic Fibrosis-related Diabetes Mellitus. June 2004.
Consensus document on managing CF-related diabetes mellitus.

Nutritional Management of Cystic Fibrosis. April 2002.
Consensus document on nutritional management of CF.

National Consensus Standards for the Nursing Management of Cystic Fibrosis. May 2001.
Consensus document on standards for nursing management of CF.

Factsheets

(Diagnosis) The sweat test in cystic fibrosis
A guide to the sweat test, what it is and how it is done.

(Diagnosis) Finding out (a guide for parents of a child newly diagnosed with CF)
A factsheet for parents of a child newly diagnosed with cystic fibrosis.

(Living with CF) Financial help
A factsheet about the financial help available for people with CF and their families, from the Cystic Fibrosis Trust and other organisations.

(Living with CF) Higher education
A pack designed for adults with cystic fibrosis intending to go on to higher education.

(Living with CF) Melioidosis and travel to tropical countries
A factsheet about melioidosis, an infection caused by Burkholderia pseudomallei.

(Living with CF) Nutrition: A guide for adults
A factsheet about eating well with cystic fibrosis.

(Living with CF) Nutrition: A guide for children and parents
A factsheet about eating well with cystic fibrosis.

(Living with CF) Nutrition: A guide for feeding infants
A guide for feeding infants who have cystic fibrosis.

(Living with CF) Housing
A pack of four factsheets on housing issues: choosing accommodation, renting, buying, and homelessness.

(Living with CF) School and cystic fibrosis
A factsheet providing information on all aspects of cystic fibrosis and school, for teachers and parents.

(CF care) A Patient's Charter: The care of patients with cystic fibrosis
Factsheet outlining the essential health care people with CF should expect to receive.

(CF care) Support available from the Cystic Fibrosis Trust
An introduction to the support offered by the Cystic Fibrosis Trust.

(CF care) Transition from paediatric to adult care: Guide for young people
A guide for young people moving from paediatric to adult care.

(CF care) Transition from paediatric to adult care: Guide for parents
A guide for parents with a child transferring to adult care.

(CF care) Transition from paediatric to adult care: Guide for commissioners and hospital / clinical teams
A guide to the transition from paediatric to adult care for commissioners and hospital and cli

(Treatment) Prescription charges
A guide to prescription charges in the UK.

(Treatment) Home intravenous therapy (Home IVs)
A factsheet on home intravenous therapy and cystic fibrosis, for patients, parents and carers.

(Treatment) Steroid treatment in cystic fibrosis
A guide to steroid treatment in cystic fibrosis, including different kinds, their use and possible side effects.

(Treatment) Physiotherapy treatment - Airway clearance
A guide to airway clearance techniques.

(Treatment) Physiotherapy treatment - For babies and toddlers
A guide to physiotherapy treatment for babies and toddlers with cystic fibrosis.

(Treatment) Urinary incontinence in cystic fibrosis
A guide to urinary incontinence in cystic fibrosis.

(Treatment) Nebuliser therapy
A guide to nebuliser therapy.

(Treatment) Totally Implantable Intravenous Access Devices (TIVADs) / ports in cystic fibrosis
A guide to the use of ports in cystic fibrosis for patients, parents and carers.

(Other CF-related issues) Cystic fibrosis and bone health
A guide to how bone health can be affected by cystic fibrosis, and the implications of this.

(Other CF-related issues) Cystic fibrosis-related diabetes
A factsheet exploring cystic fibrosis-related diabetes.

(Other CF-related issues) Lung transplantation in cystic fibrosis
A factsheet looking at lung transplantation and cystic fibrosis.

Leaflets

Cystic fibrosis... what exactly?
A leaflet offering a basic introduction to cystic fibrosis.

Cystic Fibrosis and Body Image

Cystic Fibrosis and Relationships
External publications (not published by Cystic Fibrosis Trust) written by and for people with cystic fibrosis.

Appendix XIII – Useful telephone numbers ☎

Royal Brompton Hospital - 0207 352 8121

	Extensions
Bed Manager	2417, bleep 1256
Biochemistry	8411
Bone densitometry	8965
CF Secretary	8674
Dietitian	8465
Foulis ward (adults)	8069, 4070
Haematology	8406
High Dependency Unit	2061, 8251
LCI	8233
Lung function	8910
Microbiology	8451
Nuclear medicine	
-- Bone densitometry	8666
-- Ventilation Scans	8666
Pharmacist (paediatric)	8038, bleep 7403
Pharmacy (drug information)	8901
Pharmacy (dispensary)	8038, 7777
Physiotherapy	8088, 8436 bleep 7300, 7304, 7311
Rose Ward	2411 2412 2413, 8543
Ventilation Scans	8666
X-ray (Sydney St – in patients)	2326
X-ray (Fulham Wing – clinic)	4668
X-ray PACS	8275

External numbers

CF Trust	0208-464 7211 11, London road, Bromley, Kent BR1 1BY www.cysticfibrosis.org.uk
CF Foundation (USA)	www.cff.org
Great Ormond Street Hospital	0207-405 9200
Kennedy-Galton Centre (genetics)	0208-869 2795
Public Health England Colindale	0208 327 7224 61 Colindale Avenue, London NW9 5EQ

Consultant referrals

Adult CF Unit	Dr Di Bilton	0207 352 8121 ext. 4384
	Dr Khin Gyi	0207 352 8997
	Dr Nick Simmonds	0207 351 8997
	Dr Andrew Jones	0207 351 8997
Dermatology	Dr Nerys Roberts	0203 315 8657
Ear Nose and Throat	Mr Jonny Harcourt	0203 315 7972

	Mr Will Grant	0203 315 7972
	Mr Guri Sandhu	0203 315 7972
	Mr Elliot Benjamin	0203 315 7972
Gastroenterology	Dr John Fell	0203 315 8628
	Dr Jenny Epstein	0203 315 8628
Genetics	Dr Sue Holder	0208 869 3171
	Manchester lab.	0161 701 4920
Growth / puberty / diabetes	Dr Nicola Bridges	0203 315 8695
	Dr Saji Alexander	0203 315 8695
Gynaecology	Mr Guy Thorpe-Beeston	0203 315 7902
Heart-lung Transplant	Dr Helen Spencer	0207 405 9200
Hepatology	Dr Marianne Samyn	0203 299 5818
	Prof David Westaby	0208 383 3534
Paediatric Surgery	Mr Muntha Haddad	0203 315 8696
	Mr Simon Clarke	0203 315 8696
Radiology	Prof David Hansell	0207 351 8034
	Dr Simon Padley	
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

Index

Page numbers in bold refer to drug information in Formulary.

D

E

F

G

H

I

J

K

L

M

N

O

U

V

W

X