Clinical Guidelines: Care of Children with Cystic Fibrosis

Royal Brompton Hospital

Part of Guy's and St Thomas' NHS Foundation Trust

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2023

9th edition

A lifetime of specialist care

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The 9th 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 9th editions (2001-2023) 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. We are delighted for other centres and other countries to use them with the above proviso. Patients who come to the Royal Brompton Hospital, either for full or shared care, will all be looked after using these guidelines.

The guideline can be downloaded as an APP or read online. We no longer produce paper copies.

If there are any comments, queries or errors noticed, please contact Ian Balfour-Lynn on i.balfour-lynn@rbht.nhs.uk.

These guidelines have been ratified by the New Drugs & Clinical Guidelines Group / Medicines Management Board, as well as the Antibiotic Strategy Group of Royal Brompton Hospital.

Next revision will be published in 2026 so this edition should not be used after that date. Please destroy all 2020 editions.

CHILDREN'S CYSTIC FIBROSIS TEAM
Royal Brompton Hospital

What's new in the 9th 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 20)

New sections/subsections
3.2 Home monitoring.
3.3. Normal blood pressure charts added to annual review section.
3.8 Paediatric Play Team.
4.7 COVID-19 added to Infection Control section.
6.2b DRESS syndrome added to Drug allergy & desensitisation section.
6.2d. Rose@Home concept added to section on Home intravenous antibiotics.
6.3 COVID-19 treatment and vaccination.
11.1f CFTR modulators .

Policy changes / additions:

Chapter 3 – How the service runs
3.1 Clinics.

- Video consultations for alternate clinic appointments for some patients, aged over 1 year.
- Clinics. Blood pressure routinely done on those on Orkambi (see below for annual review).

3.2 Home monitoring. New program for home spirometry, remote microbiology and blood testing to complement video consultations.
3.3 Annual review.

- We no longer do laboratory plethysmography.
- Annual review. *Blood pressure* for all aged 5 years and above. And all children on Orkambi (aged 2-5 years). Record in the letter. Normal blood pressure by age tables added.
- We are finding high levels of Vitamins A and/or E in those on Kaftrio, our dietitians and pharmacists will decide on dose reductions when results are available.

3.8 Paediatric Play Team. Section on what the marvellous team does.

Chapter 4 - Admission to hospital
4.2 Induced sputum will be carried out in non-sputum producers when no organism has been found recently and IV cefuroxime is being started.
4.5 Self Administration of Medicines. Minor changes.
4.7 Infection control . Guidance for COVID-19 added.

Chapter 5 - Making the diagnosis
5.1 Newborn screening.

- Education visit now done in a single day.
- New national algorithm for NBS added.
- Prompt sheet for health visitors contacting families is in appendix 12.
- We no longer do a routine sweat test on older siblings of babies diagnosed by screening.

5.7 Pre-implantation diagnosis. GP must make the referral to local genetic centre who then makes the referral for PGD to Guy's and St Thomas' centre.

Chapter 6 - Respiratory care

6.1 Chest exacerbations. Default for course of IV antibiotics remains 14d but consultant can decide if 10d is sufficient.

6.2a 5. IV antibiotics for unknown organisms.

- If never had *P aeruginosa* or none for 3 years we now use IV cefuroxime instead of IV meropenem. Induced sputum is carried out at start of course on non-sputum producers.
- IV antibiotics for unknown organisms. We no longer routinely use IV teicoplanin just because grown *S aureus* in past year.

6.2a 6 Ia. *S aureus*.

- Use flucloxacillin prophylaxis until CF START results published.
- Isolations. Flucloxacillin being used for 2 weeks rather than 4 weeks. Check cultures 2 weeks after finishing the 2 week course.
- Regrowths. 2nd line treatment now 10 days linezolid for those on CFTR modulators (avoiding rifampicin).
- Regrowths. Consider skin decontamination (failed eradication).
- IV antibiotics. We are reducing the use of IV teicoplanin. Use IV meropenem + tobramycin, for 2 weeks, with IV teicoplanin just in the 2nd week if grow SA despite the 1st line IVABs.
- Suggestion to replace child's toothbrush after eradication of SA as a potential source of reinfection.

6.2a 6 IIa-b. *Haemophilus influenzae*. Antibiotics being used for 2 weeks rather than 4 weeks. Check cultures 2 weeks after finishing the 2 week course.

6.2a 6 III. *Pseudomonas aeruginosa*.

- We have removed section on long term intravenous colistin as we no longer do this (due to lack of necessity).
- 1st isolation - If the child is unwell or young (under 1 year) we may decide to use IV antibiotics.
- Suggestion to replace child's toothbrush after eradication of PsA as a potential source of reinfection.
- We now use N-acetylcysteine (NAC) during all aminoglycoside courses, i.e., we have added it use with amikacin also.
- We use nebulised aztreonam twice daily, and only suggest three times a day for particularly troublesome cases.

6.2a 6 IV MRSA. 1st line treatment now linezolid for 2 weeks for those on CFTR modulators (avoiding rifampicin). If not on a modulator, remains rifampicin and fusidic acid for 2 weeks.

6.2a 6 VII. NTM.

- We will do an ECG to check for long QT due to the potential effects of azithromycin, moxifloxacin, ondansetron and clofazimine.
- We now use N-acetylcysteine (NAC) during all aminoglycoside courses, i.e., we have added it use with amikacin also.
- MAC. We have switched rifampicin to moxifloxacin or ciprofloxacin, due to interactions with Kaftrio.

6.2b. Drug allergy & desensitisation. Section on DRESS syndrome added.

6.2d Rose@Home. New program to optimise home intravenous antibiotics by having regular reviews with the whole MDT throughout the course.

6.3. COVID-19 treatment and vaccination. Current advice.

6.4a. ABPA.

- New regimen for reducing prednisolone dosing.
- Posaconazole courses are shortened (due to interactions with CFTR modulators) so we stop when the corticosteroids stop.
- ABPA. Varicella antibody results should be checked when starting someone on a long course of oral steroids.

6.4a Aspergillus growths.

- Should always be eradicated, and recurrent growths must be treated, using posaconazole for 2 weeks. Eradication must be confirmed on sputum or induced sputum.
- We no longer use itraconazole, posaconazole is 1st choice for all aspergillus disease in children aged 6 months and above.

6.4b. *Scedosporium apiospermum*. We no longer use terbinafine.

6.6. Dornase alfa (RhDNase). We will no longer offer it routinely to a 6 year old child on Kaftrio or ivacaftor, assuming they have minimal lung disease. We are going to use the generic name dornase alfa now.

6.7 Hypertonic saline. We have now decided to offer 7% H/S twice daily routinely at 1 year of age unless they are already on ivacaftor. It is likely we will stop it if they start on Kaftrio. We will check at 4 weeks how tolerating it, and if not going will try 3% saline. We will only start it in infants under 1 year if we re clinically concerned about their lungs.

6.9 Long term azithromycin.

- We will not routinely do an ECG when starting long term azithromycin unless there is a family history of long QT or the child had previously fainted/had loss of consciousness. We will do an ECG if they are taking a 2nd drug that can affect the QT interval, and when using azithromycin for NTM treatment.
- Send a sputum or induced sputum looking for NTM before starting long term AZM.
- Azithromycin. We would consider using it long term in children < 3 years with concerning lung disease.

6.10 CFTR modulators. Many changes – particularly inclusion of Kaftrio. Clarification we need AST, ALT, and bilirubin for liver checks. Clarification on dealing with adverse effects.

6.16c Inhaled drug response assessment. We do not need to repeat a DRA if a child is changing a tobramycin nebuliser generic brand, only if the drug concentration is changing.

6.16f Induced sputum.

- Will be done to check if Aspergillus has been eradicated.
- Will be done at the start of an admission in a non-sputum producer who has grown nothing and is being treated with IV cefuroxime as a single agent.

Chapter 7 - Gastrointestinal & nutritional care

7.1 Vitamins. We are getting high levels of vitamins A, D and E in some patients on Kaftrio so annual review results are being checked by the dietitians and pharmacists and dose adjustments made.

7.3 Salt supplement. For those on kaftrio with normal sweat chloride, extra salt on their food and salt supplements should not be needed routinely.
7.10 Liver disease. Introduction of Metavir scoring system for CF liver disease.

Chapter 8 - Other non-pulmonary complications of CF
8.1 Cystic fibrosis-related diabetes.

- Use of Libre device for continuous glucose monitoring.
- Glucose Control Test being trialled.

8.4 Bone metabolism. Measure parathyroid hormone (PTH) when find low bone mineral density.
8.5c Hearing. We will test for m.15555A>G mutation at the child's 1st annual review, and catch up whole clinic cohort over next 1-2 years.

Chapter 11 - Drug formulary

Additions
Kaftrio (Elexacaftor / tezacaftor / ivacaftor)
Vantobra – new nebulised brand of tobramycin

Removed
Azithromycin (prophylactic antibiotic)
Ranitidine
Intravenous immunoglobulin (section 6.13)

Dose changes
Oral azithromycin treatment (weight recommendations)
Oral flucloxacillin prophylactic dose for older children
Nebulised colistin – dose change at 2yrs instead of 8 yrs
Intravenous meropenem

New information
CFTR modulators in their own section
Linezolid – aim for 10 day courses, only do FBC if course 14d or more.
Section on salt supplements (11.2g)

Appendices
Appendix 18. Social Security Benefits. Sections on charities added.

New appendices
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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 Hospital and District General Hospitals on a network 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.

With the development of the mobile phone APP for our guidelines in 2017, we know that aside from the UK, the guidelines have been downloaded in 85 countries - Afghanistan, Albania, American Samoa, Antigua & Barbuda, Argentina, Armenia, Australia, Austria, Bahrain, Bangladesh, Belarus, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Cyprus, Czech Republic, Ecuador, Egypt, Ethiopia, Finland, France, Germany, Ghana, Gibraltar, Greece, Hong Kong, Hungary, India, Indonesia, Iran, Ireland, Israel, Italy, Kazakhstan, Kenya, Kyrgyzstan, Latvia, Lebanon, Libya, Lithuania, Luxembourg, Macedonia, Malaysia, Malta, Mexico, Montenegro, Myanmar, Namibia, Netherlands, New Zealand, Nicaragua, Norway, Oman, Paraguay, Pakistan, Portugal, Philippines, Qatar, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, Somalia, South Africa, Spain, Sri Lanka, Sweden, Switzerland, Thailand, Trinidad & Tobago, Turkey, Seychelles, UAE, Ukraine, Uruguay, USA, Yemen and Zimbabwe.

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, CF Trust, British Thoracic Society, and NHSE Service Specifications. 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, psychologists, and pharmacists. 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 NHSE National Service Specification and our signed Service Level Agreement are adhered to. We also run several out-reach clinics whereby our MDT see CF patients in their local hospitals. Details of the Service Specification can be found – https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-a/a01/.

Death in childhood from CF is now rare, and UK children born today are likely to have a median life expectancy of over 50 years (56 years in CF Registry report 2021), which will improve further with increasing use of highly effective CF modulator therapy. There are approximately 10,800 people with CF in the UK and 60% are adults. On average, large District General Hospitals will have a local CF population of between 10 and 20 patients (it may be less in the London region which has a higher density of hospitals); and General Practitioners between 0 and 2 patients. The Paediatric CF Service at the Royal Brompton Hospital has around 300 children under its care whilst there are about 650 patients in the Adult Service. The paediatric team normally sees children and adolescents until they finish their GCSEs, and they will have made the transition to an Adult CF Service at the Royal Brompton Hospital or another Specialist Adult CF Centre of their choice by their 17th birthday.

2. Our multidisciplinary team

2.1 Department staff and contact numbers

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☎ 0207-352 8121

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Dr Samatha Sonnappa	Consultant in Paediatric Respiratory Medicine (In-patient care only for CF) s.sonnappa@rbht.nhs.uk
Dr Mark Rosenthal	Consultant in Paediatric Respiratory Medicine m.rosenthal@rbht.nhs.uk (clinics only)
Dr Catherine Greenaway	Consultant in Paediatric General & Respiratory Medicine (Visiting - 2 clinics per month) Catherine.Greenaway@sash.nhs.uk
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	Laura Seddon (Monday to Wednesday) l.seddon@rbht.nhs.uk Mobile phone 07973173969
Adult CF Centre Director	**Dr Su Madge** s.madge@rbht.nhs.uk Bleep 7032, Ext 84053
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Family Liaison Service	**Laura Hill** l.hill2@rbht.nhs.uk Extension 88588
Welfare Officer	**Patricia McNamara** p.mcnamara@rbht.nhs.uk Ext 84736
Safeguarding Children Team	**Christine Harman-Collins** Senior Safeguarding Children Nurse Specialist Ext 84304 Mobile phone 07896 220697 c.harman-collins@rbht.nhs.uk
	Joanne Bowley Nurse specialist – Safeguarding Children Ext 84289 Mobile phone 07929 792359 J.bowley@rbht.nhs.uk

	Rachel Ward Safeguarding Children's Team Administrator Ext 84304, 82903, 82904, 84289 **Generic email** SafeguardingChildren@rbht.nhs.uk rbh-tr.sgchildren@nhs.net
Ward	Rose Ward Direct line - 0207 351 8588, Extensions 82411, 82412, 82413 Adult Ward - Foulis Extensions 88069, 84070, 8486
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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. If there is no reply, ask for Rose ward.

2.2 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:

Adult CF Unit - RBH	Dr Nick Simmonds Dr Andrew Jones Dr Imogen Felton Dr Emem-Fong Ukor	0207 351 8997
Dermatology – C&W	Dr Nerys Roberts	0203 315 8657
Diabetes / Growth / puberty – C&W	Dr Nicola Bridges Dr Saji Alexander	0203 315 8695
Ear Nose and Throat – Evelina	Mr Dan Tweedie	020 7188 7188 Ext 53176
Gastroenterology – C&W	Dr Krish Soondrum Dr John Fell Dr Jenny Epstein Dr Anthi Thangarajah	0203 315 8628
Genetics	Dr Deborah Morris-Rosendahl Dr Sue Holder	0207 351 8412 0208 869 3171
Gynaecology	C&W dept.	0203 315 8000
Heart-lung Transplant - GOSH	Dr Helen Spencer	0207 405 9200
Hepatology – King's	Dr Marianne Samyn Dr Sanjay Bansal	0203 299 1162 / 3214
Paediatric Surgery – C&W	Mr Simon Clarke	0203 315 8885
Palliative care - Evelina	Dr Ella Aidoo or dept.	07747267799 team mobile, or out of hours 0207 188 7188
Radiology - RBH	Dr Tom Semple Dr Simon Padley	0207 351 8034 0207 352 8121 ext. 2943
Rheumatology - GOSH	Dr Clarissa Pilkington	0207 829 7887
Thoracic Surgery - RBH	Mr Simon Jordan	0207 351 8559

RBH = Royal Brompton Hospital; C&W = Chelsea & Westminster Hospital; GOSH = Great Ormond St. Hospital

3. How the service runs

We hold Management Meetings with representation from the whole MDT every 2 months to optimise the service.

3.1 Clinics

The clinics are run in a segregation format (see section 4.7). There are 2 clinics per week, Monday and Friday – appointments are in 2 waves - 1.45pm and 3.15pm, with a 4.15pm urgent slot. In addition, new referrals of older patients are occasionally seen for the first time in a general respiratory clinic on a Tuesday am or Wednesday pm.

Children with *Burkholderia* species and MRSA do not attend the routine CF clinics. These patients will attend clinic on the 2nd Friday of the month. Patients with MRSA will be booked into earlier time slots and those with *B cepacia* having later time slots.

Patients with non-tuberculous *Mycobacteria* (NTM) complex will come to the 2nd wave of a clinic so will be the last ones in their room. No-one can use the room afterwards for at least 1 hour. Spirometry flow heads need only be changed for *M abscessus* patients.

Patients with multiresistant PsA should come to 2nd wave of clinic.

When can patients re-join the usual CF clinic?

- ***B cepacia****:* when they have been free of the organism for **2 years**, with at least 3 negative sputum or cough swabs or BAL samples per year. Caution though if the original isolation was on sputum or BAL, and subsequent samples are cough swabs only – get an induced sputum to be certain. They should then come to the 2nd wave of clinic.

- **MRSA**: when they have had 3 negative swabs (see hospital policy) https://www.rbht.nhs.uk/sites/nhs/files/Trust%20policies/MRSA%20policy%20-%20May%202016.pdf
    - 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*** **complex***:* considered 'eradicated' when they have had 4 negative samples over 1 year since their 1st negative sample. Considered 'free of NTM' *i.e.*, it has not regrown and can re-join standard clinic 1 year after eradication *i.e.*, 2 years after 1st negative sample. See also sections 4.7 and 6.2a 6.VII.

There is a joint CF diabetes clinic on the 1st Monday and 3rd Friday of the month at RBH.

Patients may attend Monday or Friday clinic at their convenience although we encourage continuity where possible. Most children are seen in CF clinic every 2 months, or every 3 months for those recognised to be well with mild disease. Infants diagnosed by newborn screening are seen monthly in the first year and sometimes more frequently in the first months following diagnosis. For some, all clinic visits are at the Royal Brompton Hospital and they must be seen 2 monthly (rarely 3 monthly) after 1 year of age. Some are seen on a

Network-care basis with a local team in their District General Hospital, and our whole MDT attends these visiting clinics. If the full team see the child -

- 2 / year locally, they must be seen at RBH 2/year (including annual review)
- 3-4 / year locally, they need only be seen at RBH once, for annual review
  This means they will be seen by the full RBH MDT at least 4 times each year. Obviously if there are difficult clinical issues then the child can be seen at RBH as much as necessary. We do not encourage children who visit from abroad annually as that is not proper Brompton care.

If clinically stable, patients may be seen as a video appointment on the NHS secure programme Attend Anywhere, alternating with face to face clinics. Annual review is always face to face. Link to the virtual clinic is https://nhs.vc/rbh-paediatric-respiratory and the parent/carer logs in with the child's name, date of birth and mobile number. Staff log in using http://england.nhs.attendanywhere.com

All out-patient visits are discussed at a weekly multi-disciplinary meeting which the consultants attend. 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. A list of the named consultants for each patient is maintained by the CF nurses and CF secretary and is available on the paediatric T drive.

The families see the following:

Doctor. This may be a consultant (Mondays – Bush, Davies, Carr, Gardner, Greenaway; and Fridays – Balfour-Lynn, Carr, Pabary, Charlton, Rosenthal), 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. HbA1c measured in CFRD clinic.

Physiotherapist. All the children should be seen by a physiotherapist to review airway clearance techniques, exercise, inhalation therapy, posture and continence; and 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 for them to be seen every clinic visit. Whilst pancreatic

sufficient patients are routinely seen at annual review, they may be seen at other clinic appointments if necessary.

Psychologists. Are available for annual reviews and may see families to commence or continue with their clinical work.

Paediatric Pharmacists. A member of the team will see those having annual review, starting CFTR drugs or if there are other medicine-related queries e.g., education, access to medicines.

Play specialist. Is available to help children to manage invasive procedures (usually blood tests) on request.

Others. The Welfare Rights Officer can also meet parents and often help guide them on how to obtain appropriate benefits to which they are entitled.

Clinic procedures

- Children over 1 year are weighed in light clothing. All children have their height measured on a stadiometer without shoes. 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 in a sitting position. 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.
- Blood pressure for those on orkambi (will be aged 2-5 years). See section 3.3 for normal blood pressure charts.
- Sputum or cough swabs are always collected for microbiology. Families are asked to carry out a cough swab at home at time of a video consultation but should only be done after proper training. Only sputum is sent for culturing non-tuberculous mycobacteria (NTM) as cough swabs are always negative for this. Culture for NTM is not carried out in every clinic but is sent at annual review, if there is clinical concern, or if the child has cultured it previously (also on all BAL and induced sputa).

Research

Consideration is always made by clinicians as to whether the child might be suitable for one of the many research projects undertaken at RBH. Participation will in the first instance be discussed with each patient and /or their parents. Expressions of interest to participate in research studies are always welcome.

Shared care clinics – Network centres

We conduct joint clinics with many of our shared care hospitals. We aim to take the full Brompton MDT (unfortunately not our pharmacists) 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. We run an annual education day with our Network Centres.

3.2 Home monitoring

The COVID-19 pandemic saw the introduction of virtual clinics and remote clinical management. Although face-to-face clinical encounters have returned, we will still operate a hybrid system of face-to-face and virtual clinics. To facilitate remote clinical care, a number of home monitoring services are available:

- Weight monitoring
- Spirometry
- Cough swabs and sputum sample collection
- Urine sodium and faecal elastase
- Capillary blood sample collection (occasionally done in older children, not routine)

Weight monitoring
The dieticians have baby scales available for newborn infants to allow regular weight measurements in the first year of life, to coincide with any virtual clinic appointments. Older children should be weighed on the day of virtual clinic appointments on home scales. Parents are encouraged to provide these themselves as there is not provision to through the clinical service.

Spirometry
All parents of children over the age of 5 years are seen in clinic by the physiology team and offered a spirometer to enable measuring lung function at home. Children will be given either a NuvoAir or Spirobank app-based spirometer together with set up instructions and contact details of the physiology team. Children are asked to do spirometry just prior to every clinic appointment or when asked to by a member of the CF team, usually if the child is unwell or we want to see if they have improved since clinic etc. Reminders to update their height on the app and perform a test session are sent via text message the day before clinic appointments. Test results come directly to a portal (NuvoAir) or are emailed in (Spirobank) and checked for technique and reproducibility by the physiology team before being uploaded onto EPR. Both the portal and email are monitored during working hours (Mon-Friday 9am-5pm). Results can be forwarded on to shared care teams via email on request. Video sessions and phone calls are offered to those who need help with the lung function technique or who are having technical difficulties. The CF CNS team are alerted to any significant drop in lung function. **It is important the height entered into the spirometers is kept up to date.**

Contact details for the respiratory physiology team: 020 7352 8121 ext. 82256
Or paedsnuvoairsupport@rbht.nhs.uk (whatever machine they are using).

Cough swabs and sputum samples
For any child attending a clinical appointment virtually, a cough swab or sputum sample should be provided in advance of the appointment. Testing kits are prepared and posted out to patients' homes by the RBH phlebotomy team; they contain instructions on how to perform the test and pre-paid postal envelopes for the patient/family to return the sample.
Samples can be requested on ICE, first by selecting the 'other services' tab on the top bar, and then selecting the 'remote testing' tab in the side on the left-hand side of the screen.
Routine tests will be made by the physiotherapy team in advance of virtual clinic appointments. Routine test results must be chased by the clinic registrar each week as part of weekly 'sputum club,' usually on Thursday afternoon with one of the CF CNS team. Any

samples not returned should be flagged and the family contacted to make sure a sample is provided.

If a home test is required outside of routine appointments, e.g., if there is clinical concern or symptoms reported by the patient/family then this can be requested by any member of staff with access to ICE. However, it is sensible to inform the CF CNS team that a request has been made, so they are aware to chase the result.

As most children do not spontaneously expectorate sputum, most remote samples requested/provided will be cough swabs. If sputum sample is needed, the physiotherapy team may be able to attempt guided sputum sample collection over video call with the patient. Discuss with the physiotherapists who will be able to guide as to whether this is possible and to arrange a call.

Urine sodium and faecal elastase
Samples for urine sodium and faecal elastase measurement can also be collected at home. These are not collected routinely but can be made when clinically indicated following virtual appointment or new clinical concern. Samples can be requested on ICE, first by selecting the 'other services' tab on the top bar, and then selecting the 'remote testing' tab in the side on the left-hand side of the screen. Selecting 'remote testing urine' will lead to 'urine sodium' and selecting 'remote testing faeces' will lead to 'faecal elastase' options. It is sensible to discuss these requests with the dieticians, so they can also chase the result.

Capillary blood sample collection
Although not in routine use, it is possible to request home blood sampling. Kits include a finger prick lancet and allow capillary sample collection only with a maximum of three tests at a time. The choice of tests available is more limited than what is available in the hospital. This service is only suitable for older children and following discussion with the child and family to be sure they are happy to do this. It may be useful for home monitoring of liver function tests, however it can not measure AST so is no good for liver function monitoring of CFTR modulators. Most children will continue to have blood tests performed with venepuncture at the time of a face-to-face appointment. Samples can be requested on ICE, first by selecting the 'other services' tab on the top bar, and then selecting the 'remote testing' tab in the side on the left-hand side of the screen. Selecting 'remote testing bloods' will lead to options of which bloods available for request.

3.3 Annual review

All patients are seen annually for a full clinical review of progress over the last year and for surveillance investigations; we try to move this away from birthday time as we are aware some children associate their birthday negatively with having a blood test. This usually takes place in the normal CF clinic, with the patient attending radiology (+/- nuclear medicine). The named consultant writes a report, although blood results must be included in the clinic letter to avoid delays to necessary changes. We are endeavouring to have a report automatically generated from the Registry with all the results and a summary, once data are entered by our Data team onto the UK CF Registry.

If a patient is admitted around the time of the annual review, all investigations take place as part of 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). When the child is next seen in clinic the AR proform (for data entry to the CF registry database) is completed and letter summarising the review and all results is sent. For patients having regular admissions, bloods will always be taken for AR so that they do not need repeating in clinic.
The children will be seen for the following:

- Discussion with the nurse specialist following the CF Registry proform. This will include the number of IV and oral antibiotic courses, usual symptoms and microbiology. Some of these data are filled in prior to the appointment.
- 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 (or faecal) stress incontinence will be reviewed when appropriate. Home air compressors for nebulisation should be brought in for yearly service. Parents must email NebPhysioEquipment@rbht.nhs.uk when they have the date for their annual review to get it booked in. Exercise testing is not routinely carried out.
- All patients are offered the opportunity to meet with a Psychologist as part of their annual assessment**.** This will hopefully explore how the child with CF and their family are managing. As per CF Trust and British Thoracic Society guidelines, both the child with CF (if aged 11 years and over) and their parents/carers are invited to complete mood questionnaires. If the families are already meeting with a psychologist, then they will not need to be seen by a psychologist at annual review unless they wish to make an appointment in advance. They will still be invited to complete the questionnaires.

Investigations

- *Lung function* - clinic spirometry is carried out as usual. We no longer do routine plethysmography unless we are particularly concerned about a patient in which case it is done when needed.

- *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. We can measure it in children as young as 4-5 years old.

  We carry this out routinely **only in children with FEV_1 ≥80%** as it is more time-consuming to perform in those with poor lung function and we find we do not get any extra clinically-useful information. Subject to the above, LCI should be a routine part of the annual assessment and is undertaken in all children aged 5 years and above. Additionally, the test can be useful in children who supposedly have 'poor technique' with spirometry leading to lower than expected lung function; if the LCI is abnormal this would indicate the low lung function is genuine and not due to technique. LCI should be booked through Sam Irving (ext. 88233, email s.irving@rbht.nhs.uk) and is carried out in Fulham Wing 1st floor.

  The higher the LCI, the worse is the distal gas mixing. Normal ranges for LCI are device-specific so it is important that the device used is recorded alongside the result, and the same device (where possible) is used when a patient has a subsequent LCI.
  In general, a value > 8.0 is above the normal range and >10.0 is significantly abnormal (we do not often have values >12).

- *Ventilation scan* is carried out in children too young to perform formal lung function. This is done in Nuclear Medicine Department, Level 3 Chelsea Wing and takes 1 hour. Ext 88666.

  What to do with an abnormal ventilation scan
  Our internal audit has shown that children with just one abnormal ventilation scan in the first 5 years of life will have a slightly lower lung function at 6 years than those that have normal pre-school scans. We therefore treat all abnormal scans even in well children. All will receive a minimum of three months of a muco-active agent, either dornase alfa or hypertonic saline. If unwell at the time of the scan, antibiotics should have been given already. A repeat scan at 3-4 months will be arranged, if normal a decision on continuation of muco-active agent will be made in clinic. Always consider whether a bronchoscopy is required. If still abnormal, more aggressive IV antibiotic treatment will be considered as well as long term muco-active agent. We do not consider the % distribution between the two lungs.

- *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 as screening at **10 and 15 years** of age. If abnormal, we consult with Dr Bridges or Dr Alexander and decide when to repeat (usually 2 years later). DxA dept no. is 88965.

- *Continuous glucose monitoring System (CGMS)* is carried out in all **10 and 14 years** of age patients as a screening procedure for CF-related diabetes, in addition to those considered to be at increased risk or where there is clinical concern of CFRD (see section 8.1).

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

- *Blood* is taken by the phlebotomist (or doctor). The default is for blood to be taken at RBH as when taken in the local hospitals, we often find some tests were not carried out, and, we do not have an instant record on EPR of previous bloods that can be compared on a trend plot. Bloods can be taken locally when the child has a significant problem with needles if that helps them. We take15 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, SBR, γGT)
  - Random glucose and glycosylated Hb
  - Vitamins A, D & E

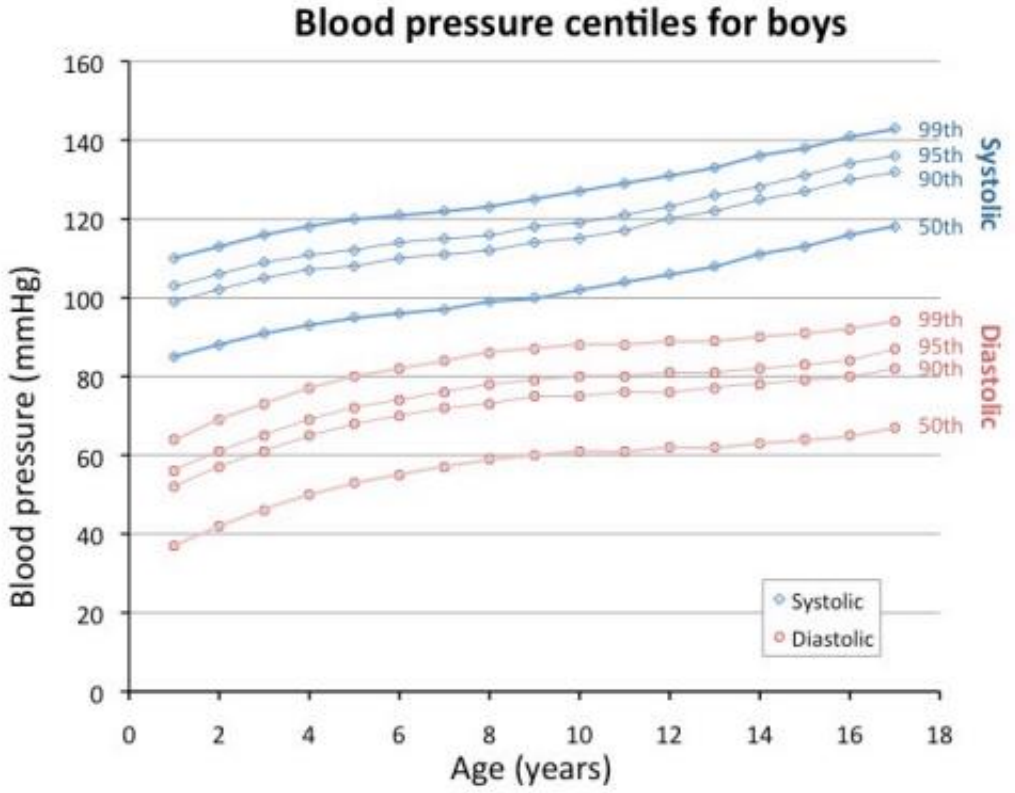
- Serum ferritin
- IgG, IgA, IgM
- Total IgE
- Aspergillus specific IgE
- Aspergillus IgG (ICAP)
- Varicella antibodies at 6th birthday [DO NOT FORGET THIS]

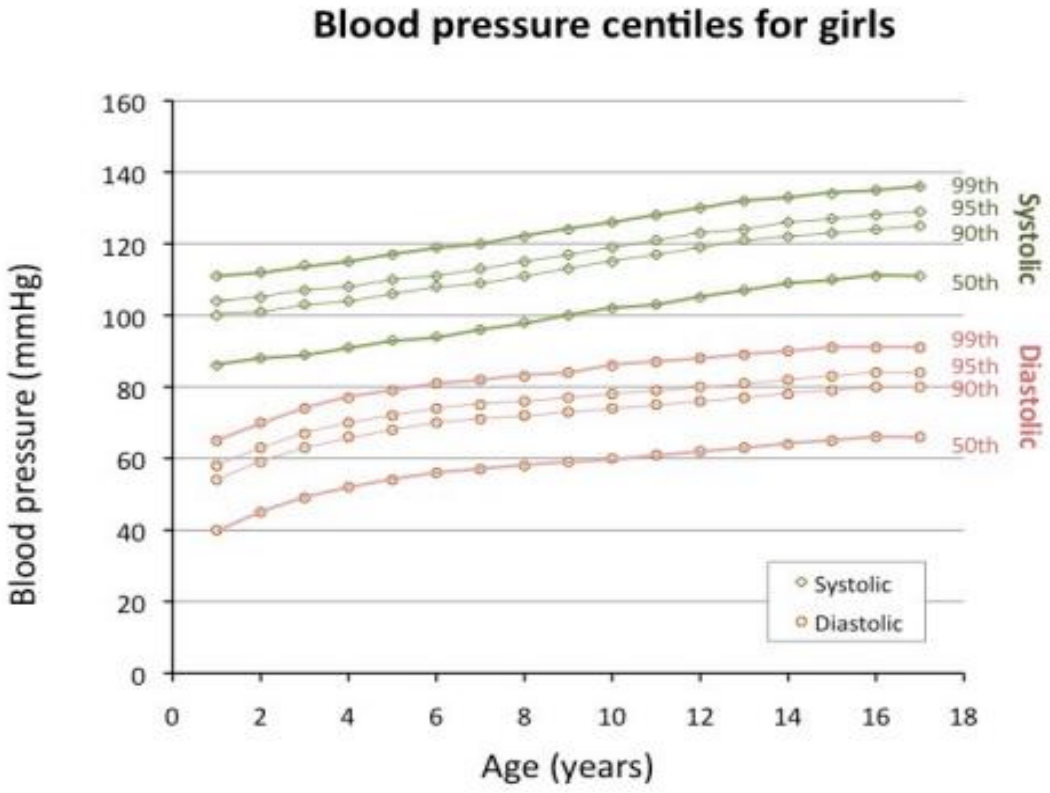
Blood bottles: 2 (red) EDTA bottles, 4 (brown) SERUM bottles (6 in older children), 1 (green) COAGULATION bottle. Bottles must be full. Use larger bottles in older children.

- *Urine* – dipstix for glucose for all with CFRD and anyone on oral corticosteroids.

- *Blood pressure* for all aged 5 years and above. And all children on Orkambi (aged 2-5 years). Record in the letter.

  Normal Blood Pressure charts taken from Edinburgh Renal Unit (www.edren.org).





Annual Review Letter

A normal clinic letter should be dictated by the doctor who sees the patient, with available investigation results **including blood results.** Results of lung function should always be reported in litres in addition to %predicted values. A report of the AR including all investigation results will be compiled by the patient's lead consultant when the results are available. Blood results will be checked within 1 week. We are still working on producing an automated report via the CF Registry.

UK CF registry

All data is entered on to the UK CF national registry, for which the parents will have given written informed consent. Data entry is critical as it determines patient banding and payment to the hospital via the PbR system. If parents decline consent to CF Registry, we calculate annual review banding for that child, and it is sent to RBH commissioning dept.to be passed onto NHSE. Website – https://cfregistry.org.uk/pages/home.

3.4 Transition from paediatric to adult care

Transition from paediatric to adult care is discussed with all patients and their families from diagnosis and at every annual review. A more detailed discussion takes place from 14 years and a letter is sent to both parents and the young adult. We aim for transition to take place at the age of 16 after GCSE exams. The transition process has been divided into two parts: pre-transition and transition. Invitations to attend a pre-transition clinic are sent to all young adults and their families at 14 and 15 year of age, so they now have 2 pre-transition visits. This is an opportunity to meet the adult CF team and ask any questions before attending the

transition clinic. We will provide information about growing up with CF, the similarities and differences of adult care and an overview of the adult CF service. The Adult CF Clinic at the Brompton Hospital may not be the Centre of choice for some patients – advice is given on how to access other services with contact details for each centre. Either way we will make the necessary referrals.

Most patients will transfer at some stage after their 16th birthday, depending on the individual and family circumstances. However, we plan to transition all young adults by their 17th birthday at the latest. The Transition Integrated Care Pathway (TICP) is commenced at this time (Appendix 1). The document detailing family, social and clinical history is completed by each patient, their family, clinical nurse specialist and the rest of the MDT. The adult team can access this document prior to the transition clinic (Appendix 1). There is a section entitled 'all about me' which we like the young adult to fill in as a way of introducing themselves to the adult team. **The original laboratory report of the genotype must be attached to the ICP.**

Transition clinics are held on Monday and Friday afternoons in the usual paediatric clinic area. There are about 6-8 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 patients remain under the care of the paediatric team until they are seen for the first time in the adult clinic, we aim for this to be 8 -12 weeks post this clinic.

It is problematic if a young person keeps missing their transition appointment. If that happens, they will be sent an adult clinic appointment, as moving to the adult service cannot be delayed unnecessarily.

Following each transition clinic an adult CF clinical nurse specialist will arrange each patient's 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 regular paediatric/adult transition meeting is held where CF nurse specialists from both services meet to discuss all patients attending the following transition clinic and to discuss issues arising from patients who have recently made the transition to the RBH adult CF service. After making the transition to the adult CF service, adolescents are initially followed up closely by the Named Transition Nurse (based in the adult unit) - the 'Named worker' as per NICE guidelines - to ensure that the change of CF team to make sure the young person and their family are well supported as they transition into the adult service.

If or when patients need admission to Foulis ward (the adult ward) the named transition nurse will visit them on alternate days to support the patient and their family throughout their first admission. There is also some support available from the hospital school particularly for those who are in continuing education or need careers advice. Young adults are supported if it is necessary for them to take exams whilst an inpatient.

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). Part of the contract also includes a list of what patients can expect from the CF team.

3.5 Homecare & Outreach Service

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 comprises 4 children's CF nurse specialists and 2 physiotherapists specialising in providing homecare for children with CF and their families. In addition, one of our dietitians and psychologists will occasionally do home visits. Criteria for referral are that RBH is the child's 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 4pm will be answered the same day (weekdays) where possible.

Nurse specialists

Laura Seddon	07973 173969
Karen Henney	07971 224068
Katie Dick	07773 964573
Caroline Devon	07483 338160

Physiotherapists

Emma Dixon	07970 269452
Nicky Murray	07791 584749

Purpose of visits

Since the COVID 19 pandemic the service has evolved to a hybrid model: offering a combination of virtual and face to face visits. Physiotherapy criteria for decision making on virtual/face to face visits are listed below.

Category	Activity
Essential for Face to Face	• Auscultation • Palpation of chest • Teaching iPEP • Teaching new ACT (AD, oscillating PEP, PEP) • Child protection and safeguarding concerns (where joint visits are essential and social distancing not possible staff need full PPE). • New set up of NIPPV for ACT or overnight • Concerns regarding development – to assess tone etc. • Any child that for whatever reason does not engage with virtual platforms • Families who do not have access to appropriate technology.
Preferred Face to Face	• iPEP/PEP review if no home manometer • New nebuliser tech review • NBS introductory visit • Review of Intermittent Percussion and MPD
Either Virtual or Face to Face	• General ACT review • General nebuliser review • Supporting ACT review on IVABs • General review of NIV for ACT or overnight • General review of HFCWO and MI:E • Transition visits • General development assessment • Spirometry technique • BDR • SUI education, support and review • General family support • Assistance with adherence to treatments

- Monitoring and assessment:
  - between routine appointments
  - following a course of oral antibiotics
  - before, during or after a course of IV antibiotics
  - at the discretion of the MDT
  - lung function and collection of specimens may not be the main purpose of the visit since the advent of home monitoring (but may be carried out in addition)

- Flush portacaths / change portacath needles (nurses only)

- Education, reinforcement and encouragement following:
  - diagnosis
  - diagnosis of new complication
  - commencement of new treatments
  - preparation for transition

- support with adherence to treatments
- school/nursery education

- Newborn Screening
  - The screening labs inform the CF nurses of babies who have been screened as 'CF SUSPECTED'.
  - The homecare nurses, with support from local health visitors, visit the families at home to inform them of the suspected result.
  - The homecare nurses can answer parent's questions with specialist, up to date knowledge.
  - Parents are given an appointment for their baby to attend RBH the next day for a sweat test where they will meet with the Consultant and a formal diagnosis made.
  - A physiotherapy homecare review will be offered within 4-6 weeks
    - Training of local teams

- 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
  - infant massage.
  - support with education for school trips

  Home/virtual visits are valued, strongly encouraged and 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. We aim for visits to be no longer than one hour whenever possible. 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. 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; however repeated refusals of visits will be discussed further within the team, and in some circumstances may be escalated to the safeguarding team. Home or virtual visits should not be allowed to be a substitute for regular clinic attendance. The psychology team and dieticians are also able to offer occasional community visits depending on the needs of each individual family.

  Liaison

  The team aims to establish links with local services as appropriate to each individual child 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 and joint working occur when necessary with community children's nurses; health visitors; school nurses & teachers; GPs; practice nurses; social workers; safeguarding teams; community physiotherapists; community dietitians; local emotional well-being /mental health services (*e.g.*, school counsellors, child and adolescent mental health services - CAMHS).

- The nursing team are available to visit GP surgeries 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 to educate school staff regarding CF and the needs relating to the child during their school day. The homecare team will also train teaching staff 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 attends shared care clinics and acts as a resource for shared care teams
- Parent Support Groups are offered where possible which are facilitated by the homecare team
- The homecare team work closely with the hospital-based team, attending MDT meetings, clinics and ward rounds where necessary. They have direct access to medical advice at RBH at all times and will consult with medical staff from the home as appropriate.
- The safety of the child is paramount, and the homecare team have regular meetings with the safeguarding team.

3.6 Clinical Psychology

Paediatric psychologists have specialist knowledge in child development and emotional and behavioural difficulties in children. They have expertise in working with children and families who are having to adjust to difficult situations such as physical illness.
The psychologists are part of the CF team. They offer a service to children with CF their parents and/or carers, their siblings, and other family members. The psychologists provide a service to both inpatients and outpatients (and offer occasional community visits, depending on the requirements of the family. They are available during CF clinics if required (it is always advisable to contact the psychologist directly prior to the clinic appointment to ensure that they have enough time available). They also offer a consultation service to other members of the CF team both at RBH and at shared care centres, and to colleagues from other statutory and voluntary agencies given consent from the patient or their parents. The psychologists attend ward rounds and other multidisciplinary meetings. Psychologists recognise that CF can affect a child and/or their family in a variety of ways. They offer the opportunity to discuss things 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, psychologists can offer suggestions for change and practical ways for coping with difficult situations such as managing invasive procedures (*e.g.*, blood tests). Any assessments and interventions carried out would be made sensitive to the needs and wishes of the child and their family. Confidentiality is respected and discussed with each person seen as it can often be helpful to share some information with other members of the CF team. Depending on the age of the child, permission from the person identified as having parental responsibility would be sought prior to a psychologist working with the child unless there were very exceptional circumstances.

Sometimes the psychologists will liaise with local counselling/mental health services because long term follow up is often better for the patient/family member carried out nearer to the family's home, or the degree of concerns about the child with CF and /or their family member (*e.g.*, severe clinical depression) is such that more specialist assessment and/or intervention is warranted. This would not be done without the permission of the patient and/or their family.

Some reasons for referral or consultation include:

- Meeting the family during the new patient education visit at the hospital, usually following newborn screening. This meeting is to introduce the psychology service, as we are aware that a new diagnosis of CF or change of hospital care can present as a challenge to any family.
- Thinking with the patient or a family member about talking with family, friends and people who work with a child with CF (*e.g*., teachers) about CF and managing their reactions to this.
- Helping a child patient to manage medical treatments *e.g*., to swallow tablets whole.
- Checking and informing (often with a medical or nursing colleague) the understanding the child has about their CF.
- Consideration of future treatments that may be offered along with the implications.
- Occasionally supporting play specialist team colleagues to support a child manage to co-operate with invasive procedures they require - including blood tests.
- Challenges which may occur with the patient's feeding behaviour/nutrition.
- Life changes related to CF care *e.g*., transfer to adult CF services, change in treatments, consideration of possible transplantation.
- Life circumstances related to the young person or family such as new sibling, new house, stressors affecting family relationships.
- Thinking about school *e.g.*, returning to school after long periods of absence for example post pandemic; changes of school placement such as transfer to secondary school; and other school related challenges such as difficulties with peer relationships or helping to identify learning difficulties.
- Problems which may or may not have something to do with CF *e.g*., toileting problems, neurocognitive challenges (e.g., ADHD/autism).
- Mood/behaviour problems which may or may not have something to do with CF. As previously documented at all CF annual assessments we aim to monitor the young person's (4 years and above) and their main carers' mood and behaviour to identify and offer support for any challenges.
- Any other challenges which may or may not be attributable to CF.
- Support for parents and other family members (as above).
- Adjustment to CFTR modulators. The advent of CFTR modulator therapies has, without doubt, been significantly positive from psychological as well as physical perspective for up to 90% of people with CF and their families.

There is emerging evidence that for some there have been challenges with emotional adjustment to these new treatments and that intervention from psychology could be supportive at this time. These challenges can include:

- Negotiating understanding of self/ their child as being more 'well' with a different future. Including consideration whether to take the medications as a result of how this may change their sense of self.
- Feelings of 'being left behind/missing out' for those currently ineligible for these medications.
- Feelings of 'survivors' guilt' for those parents and patients who have been part of the CF community for some time and know others, including older family members, who may not have had opportunity to maximally benefit from the medications. Also, global disparity of provision of the medicines.
- Thoughts of the burdensome nature of other (symptom management) treatments for CF and the effect that this may have on treatment adherence.

- Challenges with body image /feeding behaviour due to changes in dietary requirements (less required resulting in undesired weight gain).
- A *small number* of patients have reported significant iatrogenic mental health symptoms directly from the CFTR medication itself. Including, significantly raised anxiety/depression (especially for those who had experienced these symptoms prior to commencing the medication), 'brain fog'/difficulties concentrating, and sleep disturbances.

3.7 Safeguarding Children Team

The Safeguarding Children Team based at RBH, deliver advice and training to all staff, as well as support to families across the Trust to ensure the safety and welfare of children and young people. They are members of the multidisciplinary team and will support staff to make appropriate referrals to Children's Social Care (CSC) within the child's local authority if concerns are identified or further support is required. Examples are:

a) when a child is seen as being a 'child in need' because of his/her disability, or because his/her health and development is likely to be significantly impaired, or further impaired, without the provision of services (Section 17, Children Act 1989).
b) when a child is suffering or is likely to suffer significant harm (Section 47, Children Act 1989).
c) where emerging problems and potential unmet needs have been identified for individual children and their families, 'Early Help' interventions are offered through multi-agency referrals (Working Together to Safeguard Children, HM 2018).

All NHS providers are expected to comply with legislation and statutory guidance, this includes:

- Children's Act 1989, 2004.
- Compliant with statutory guidance *i.e.,* Working Together to Safeguard Children (2018) and Section 11 of the Children Act 2004.
- Meeting Care Quality Commission (CQC) Essential Standard for Quality and Safety – Outcome 7.
- Safeguarding Children & Young People: Roles and Competencies for Health Care Staff (RCPCH Intercollegiate Document 2014).

Overall remit of the Safeguarding Children Team:

- To be the point of contact for all safeguarding children concerns throughout the Trust. See appendix 16 for pathway & contacts.
- Assess and analyse family strengths and difficulties in complex cases in conjunction with staff, children and their families, particularly regarding family history and family functioning, using risk assessment tools.
- Supporting staff in the collation of evidence of concerns and in developing safeguarding chronologies and in supporting staff with report writing.
- Supporting staff to make referrals to CSC for safeguarding concerns.
- Offer training and guidance, as well as regular team or one to one safeguarding supervision to all paediatric staff.

- Identifying children and young people subject to Child Protection Plans (CPP), Child in Need Plans (CIN) or who are Looked After Children (LAC), with early liaison with the relevant multi-agency team.
- Ensure that RBH is adequately represented at appropriate strategic, core groups, conferences and professionals' meetings as well as Team Around the Child/Family meetings. This may include the Safeguarding Team attending with staff to offer support where required.
- Supporting families with no recourse to public funds or who are homeless, by liaison with appropriate CSC or local services to ensure that the safety and welfare of the child remains of paramount importance.
- Attend regular child related meetings within RBH, where necessary to offer support and advice.

3.8 Paediatric Play Team

Play is an essential part of childhood and is the bedrock for all development. It can also be used to provide preparation for procedures, with distraction, coping strategies, and support to better understand and tolerate the procedure. This leads to better co-operation and a higher success rate so that sedation is required less often.

The RBH Play Team run a 7-day a week service with staffing to support children of all ages and stages of development. We are a team made of qualified and registered Health Play Specialists and Play Assistants. We work both with inpatients and outpatients to provide continuity of care and support with an aim to build a relationship with the families throughout childhood.

Besides staffing a playroom and sensory area, which includes a provision to support more than one child with CF at a time, we offer a range of services to support children on their hospital journey throughout their childhood.

- We can offer support with needle anxiety, with workshops, desensitisation, and one to one support. We provide support for insertion of vascular lines.
- We work closely with the radiology, Nuclear Medicine, MRI and the nursing/medical teams to provide support for CT scans and other essential investigations.
- We run a 'pill school' to help young patients with taking oral medications.
- We create programmes to provide pre-admission support to help the child's (and family's) expectations and understanding of what the admission entails.

Our aim is to provide an inclusive service to engage our patients and families, enhancing their hospital and clinic experience.

3.9 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 can help families if problems arise either in hospital or at home. They can also liaise with other 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 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.

4. Admission to hospital

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

- Education of the family at time of new diagnosis.
- Specific investigations *e.g.*, bronchoscopy, pH study.
- 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 methylprednisolone (usually 3 nights).
- Elective operations *e.g.*, portacath or gastrostomy insertion, ENT or dental operation.
- A complex presentation of a child with CF *i.e.*, symptoms and the effect that this has on their daily functioning which would warrant very close observation for a period by the CF MDT.

We have found a decrease in hospital admissions since the introduction of highly effective modulator therapy.

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.

Occasionally a child and / or their family have very particular needs (*e.g.*, the child has autistic spectrum disorder) or have had a very challenging previous experience with an inpatient admission at RBH or another hospital. In these circumstances a plan ('Pre-admission Plan') is constructed which serves to document the needs and/or expectations of the child and their family and of the inpatient CF services at RBH to promote a successful admission. This might include the need for specific team members *e.g.*, the Play Specialist team for procedures and advance planning, and inclusion of all relevant teams will allow greater success.

We also have Pre-admission form to be filled out by the person arranging the admission. This gives guidance to what IV antibiotics should be used, and any special instructions for specific investigations to be carried out (appendix 3).

Informing the PICC team via email (see section 4.3) and requesting the PICC access on EPR in advance is important and will reduce delay.

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. All subsequent documentation for that admission is entered on continuation sheets as part of the

ICP. The folders are transparent white in colour on Rose ward. Medical admission paperwork covers the following information.

- **Reason for admission** (tick box).
- **Current CF complications** (tick box).
- **Date of last admission.**
- Date of **last chest exacerbation**, last oral antibiotic course.
- **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), and timing (days of IVABs). Check it is also written on the front cover of the notes.
- **Liver function abnormalities** due to IV antibiotics.
- **Past history of ABPA** - (if applicable) should be recorded with most recent total & aspergillus-specific IgE, together with maximum values in the past year for comparison.
- **Current medications** -
    - A full drug history including the types of inhaler used *e.g.*, turbohaler, MDI with spacer (with or without a mask) etc., is mandatory. Inhaler technique must always be checked.
    - Document if the patient is on a CFTR modulator (e.g., kaftrio), including starting date.
    - 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 or hearing/balance issues.
    - **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 it 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 hospital.
        - The same applies to dry powder inhalers.
    - Drug histories are confirmed by a pharmacist or pharmacy technician at the earliest opportunity within pharmacy opening hours.
- **Last sputum/cough swab obtained.**
- **Is annual assessment due soon?** If so, investigations should be arranged during admission (see section 3.3).
- **Best FEV_1% and FVC% in last year.** Absolute (litres) as well as % predicted values must be recorded. These can be found from clinic letters/EPR and the lung function trend over time is available on the T drive\Paediatrics\Lung Function Trends. **Note, it is possible to view uploaded results on the current EPR system by applying filters [select filters tab on EPR, 6th along the top and select 'Respiratory Function Tests HH' – even for Royal Brompton Patients].**
- **Documented concerns about weight and height.** Electronic longitudinal growth charts can be found on EDM. Growth trend over time is available with the lung function on the T drive\Paediatrics\Lung Function Trends. A paper chart for weight during the admission is 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* complex require specific action with regards to therapy and isolation from other CF patients.
- **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. Also, whether social care has been involved in supporting the family either currently or in the past, and/or whether the family have worked with psychology services in the past and/or currently.

Consent for use of IV aminoglycosides.
See section 6.2a 6 IIIe. All parents/children who will be receiving IV aminoglycoside antibiotics should be given time to read the dedicated **written consent form** (see appendix 4) before discussing the issues with the medical team. Should they consent, this should be signed in the presence of the medical team and filed in the patient notes. Should the parent/child not consent, a decision on an alternative antibiotic regimen should be made by the SpR or consultant for the ward. Consent must be taken at the start of admission before any IV antibiotics are given. Do not forget to start N-acetylcysteine (NAC) when prescribing any IV aminoglycosides (see section 6.2a 6 IIIe) which continues until discharge.

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 in 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. Growth chart should be in notes and on EDM.
- Height (cms & centiles).
- Head circumference in <1 year olds.
- Temperature, heart rate, respiratory rate.
- 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 at weekends** (use the child's home or 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 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 (will last up to 5 hours). You can also use Cryogesic spray (ethyl chloride) which is used immediately before the procedure but is only suitable for very short procedures (some children prefer this). Please always check with the child and family if coping with bloods and/or needles has been challenging in the past – if so, there is likely to be an existing support plan for coping with blood tests on the patient's Electronic Record. If there is no existing plan or additional support to the plan is required, please discuss this with a play specialist or a psychologist in advance for help and support, and if necessary, defer testing unless it is urgent.

If the child is due annual review (usually within 3 months after birthday) within 3 months, make sure all annual review bloods are taken (add immunoglobulins, serum vitamins, clotting) on day 2 when aminoglycoside levels are taken - see list in section 3.3. Remember to arrange other tests if required - chest x-ray, liver ultrasound or DEXA scan, and arrange formal lung function and lung clearance index (LCI) for the final week of the admission.

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 specific IgE**	**serum (brown)**	
• **CRP**	**serum (brown)**	
• **Aspergillus IgG**	**serum (brown) - 1ml**	***Virology/Immunology***

There are care-sets on ICE requesting platform that encompass the above tests, labelled as 'CF Admission (paediatric)' and ' Paediatric CF Annual Review' (more extensive list). These can be found on ICE → Requesting → Profiles RBH tab → Paediatric CF tab. NOTE – this will change when APOLLO system introduced in 2023.

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.
Induced sputum will be carried out in non-sputum producers when no organism has been found recently.

Nasopharyngeal aspirate for viral detection is sometimes indicated (usually <1 year old).
Viral swabs can also be used in older children, the back of the throat needs to be swabbed to obtain cells. These may also be used to detect COVID-19.
Urinalysis must be performed on admission especially if the child is on oral steroids or if recent history of weight loss.
Urine sodium - also useful for all patients, to guide sodium supplementation. This is especially important in the summer and in those with growth concerns.

Further investigations during admission:

- Twice weekly sputum/cough swab, and at point of discharge.
- Daily SpO_2 unless initial one >95%.
- Twice weekly spirometry (Monday, Thursday).
- Twice weekly weight (Tues, Fri): 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 study (Masimo) early in admission, especially if FEV_1<50% or resting SpO_2 <92% (see section 6.17).

Drug monitoring – MUST NOT BE TAKEN FROM LINES/PORT

Aminoglycosides (tobramycin, amikacin)

- Pre-dose levels 23 hours after 1st dose (*i.e.*, before 2nd IV dose). These are sent in a serum (brown) bottle to biochemistry. If in desired range, repeat 1 week later; and 1 week after that if having 3 weeks antibiotics. See section 6.2a, part 6.IIIg.
- Drug level timings should be prescribed on electronic drug chart at admission.

IV Colistin

- Once weekly U + Es.

Chloramphenicol

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

Linezolid

- No blood if course less than 14 days. If 14 days or more, then weekly FBC.

Itraconazole

- Monthly LFTs + drug level if indicated (*e.g.*, an interacting drug is commenced, efficacy is not observed, or toxicity is suspected). See section 6.4a.

Posaconazole

- Monthly LFTs + drug level to be taken after at least 1 week of commencing therapy or dose changed, if an interacting drug is commenced efficacy is not observed, or toxicity is suspected. Take sample just before the next oral dose. See section 6.4.

Voriconazole

- Weekly LFTs for the first month then monthly thereafter + monthly U&Es + drug levels should be measured at least 3 days after commencing therapy or dose changes, if an interacting drug is commenced, efficacy is not observed, or toxicity is suspected. Take sample just before the next oral dose. See section 6.4.

Note: If the patient is on a CFTR modulator and is being started on an anti-fungal agent, please check with Pharmacy regarding the changes in dosing required for the modulator (likely to be reduced for the duration of the anti-fungal treatment).

4.3 Venous access & PICC/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 access the portacath with a gripper needle on the child's admission. Otherwise peripherally inserted central catheters (PICC) are our preferred method of access. There are occasions when a short cannula or peripherally inserted long line 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.

PICC lines are inserted by the radiology department and doctor or nurse specialist arranging admission should sort this in advance of the admission.

- Fill in details on ICE (or access requests via EPR)
- Phone radiology 82326
- Email usually Bruce Barton (b.barton@rbht.nhs.uk) or Nelly Samchkuashvili (n.samchkuashvili@rbht.nhs.uk).

These lines are generally inserted under ultrasound guidance in the radiology department, assisted by the play team if necessary, but only Monday to Fridays 9-5. We try to avoid them being inserted under general anaesthesia. They do not need chest X-ray to confirm placement unless specifically requested by the inserting professional. These PICC lines can often be safely used for blood taking during the admission (but NOT for drug levels when the drug is delivered through the line).

Please note that sometimes patients are on the bronchoscopy list for PICC lines and so awareness of any delays is important, especially if the patient is fasted. Timely communication with the family is important.

Whatever grade of doctor, **no more than three attempts of line insertion** should be tried before asking for additional support from colleagues. We understand from research and talking with our patients that the line insertion can often be the most challenging part of their admission. We also appreciate that if this feels challenging for the child/family this can often set the tone for a difficult admission, and future problems. As such, if children have reported that venous access may be difficult for them then please identify whether there is a support plan already in place on the child's electronic patient record or ask a play specialist and/or psychologist for support (see below). Similarly, should 'therapeutic safe holding' (restraint) be deemed necessary for the insertion of a line for any child older than a toddler please ensure that a play specialist is informed and that strategies are employed to prevent and / or mitigate the necessity for this.

Some children will require sedation prior to PICC or long line insertion. In suitable children, **Entonox** (50% nitrous oxide / 50% oxygen) should be the first choice. Relevant contraindications are pneumothorax and intestinal obstruction. Please note that the patient should have an empty stomach prior to the procedure to reduce the likelihood of nausea and vomiting, they must be **nil by mouth for 1 hour** (we do not require 6 hour fasting) - see separate guideline for its use available on our intranet in Clinical Guidelines section. Entonox is not used by adult service due to risk and therefore any child or young person who uses it will need to learn to manage without by transition to adult CF service.

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 oral sedation need written consent and must be kept nil by mouth as follows -

- Bottle milk, solids - 6 hours
- Breast milk - 4 hours
- Clear fluids - 2 hours

Vein selection is made taking the needs/request of the patient (*e.g*., to try to access right arm if they are left handed) into account. Local topical anaesthesia should be offered (EMLA).

For long line insertion, we currently use Vygon Nutrilines which are 30 cms in length and available in 2 French (24 gauge inner lumen, 0.6mm external diameter) or 3 French (20 gauge inner lumen, 1 mm external diameter) sizes. As a general guide 2 French lines are suitable for infants and 3 French lines for those > 1 year old. Veins in the antecubital fossa are the preferred sites of insertion (preferably the side the child does not use for writing). Prior to insertion, 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 (*e.g*., chest x-ray done to check position of pH probe), 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 (ChloraPrep) swab stick x 2
- Non-toothed forceps
- Sterile scissors
- Sterile gauze & Steristrips
- Clear sterile dressing (IV 10000 or Tegaderm depending on the child's allergy status)
- 10ml 0.9% saline
- 10mls heparin saline (10 units heparin/ml)
- 10ml syringe
- Green needle
- Bionector
- Bandage
- Biopatch

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 re-advance 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 heparinised 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 adding a Biopatch to the insertion site and covering the whole dressing with a bandage.

If inserted without ultrasound control, do a CXR to check position (i.e., not gone too far - into the heart or up the neck). No need to do CXR when ultrasound confirmed position.

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. If taking blood this way has become necessary for the patient, please inform the medical team and document this. Patients may be used to this from other centres, although our network centres should follow our policies. Regardless of this, blood aminoglycoside levels must NEVER be taken from portacaths or longlines.

Consider use of alteplase or urokinase if long line or portacath are blocked (see section 6.2e).

4.4 Procedural distress

Preparation and planning with the child and family is essential to understand how the CF team can best help them to cope with any invasive procedures and treatments. A play specialist is routinely offered to support all children. They can offer guidance to support understanding and co-operation, also providing distraction tools and coping strategies to provide the best possible experience. The following are some suggestions for managing an

invasive procedure in all cases, and especially when you know that the child or young person is feeling very anxious:

- Ask what has helped previously if/when the child had a good experience.
- Talk to the parent/carer accompanying them about their role, *i.e.*, do they themselves have any fears or anxieties about the procedure, who they want to come into the room (often as few people as possible is most useful), who will hold the child, positioning the child, soothing the child and above all modelling calm themselves. In all preparatory conversations with the family, normalise any anxiety they express, and be empathic (*i.e.*, "It's understandable you feel worried/scared etc.").
- Encourage child to occupy themselves beforehand (gentle exercise, attend hospital school *i.e.*, not to sit feeling anxious for an hour before).
- Encourage child to keep warm (not become chilly).
- Encourage child to drink a lot of fluids (to not become dehydrated) – unless nil by mouth.
- 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.
- Make an agreement with the child about how many attempts you will have and do not exceed it. This may mean that you must take a break and try again later.
- Consider the timing of procedures, as far as possible keep to the agreed time and do not leave the child waiting beyond this.
- If at all possible, do invasive procedures in a dedicated treatment room (not the child's cubicle/playroom etc.).
- Make sure all equipment is ready before you get the child into the treatment room.
- Make sure that the child has been to the toilet and removed Tagaderm and EMLA prior to entering the treatment room to avoid delaying tactics.
- 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, and praise accordingly.
- 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.
- At the end of the attempt, (successful or not), praise even small signs of coping/trying that have been observed.
- Use of supportive holding (previously been known as restraint) warrants planning and agreement with the MDT and family unless the procedure is deemed urgent.

Reference - Good Practice Guidelines: Evidence-based guidelines for the management of invasive and/or distressing procedures with children. British Psychological Society March 2010.

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/parents/carers who may require additional support or other strategies to ensure adequate pharmaceutical care in the home. The SAM scheme is only intended to operate in the in-patient ward setting.

Full details are available on the intranet, the latest version is published June 2022. To search, go on the following link - Medicines Management Policies, Procedures and Guidelines. Then type SELF in search box, and the children's and adult policies are shown.

The SAM policy

All CF patients/parents/carers responsible for administering their own medicines at home are considered. The decision to is discussed with the CF multi-disciplinary team on the daily ward round and they are given the information sheets (intranet policy appendices 1 & 2). Signed consent is obtained (intranet policy appendix 4).

Exclusion criteria

- Patients <12 years or those not deemed capable following assessment may not administer drugs themselves. However, they may be included in the scheme if their parents/carers are assessed as competent and are resident with their child at all times.
- Parents who would benefit from further observation and/or education in use of the medications.
- Patients with unstable medication requirements.
- Patients/parents/carers who are unwilling to agree to participate.
- Patients/parents/carers who are clinically confused or who are expressing suicidal/self-harm tendencies. Those with a history of drug or alcohol abuse may only be included with extra supervision.
- Children on High Dependency Unit.

Medications included in the scheme

- Medicines suitable for the SAM scheme are those the child was taking prior to admission, and those that will be continued on discharge.
- Intravenous medications are only self-administered when the patients/parents/carers are being trained to administer home intravenous antibiotics.
- Routine oral medications included pancreatic enzyme replacement, vitamins, antacids, long term antibiotics, ursodeoxycholic acid, laxatives.
- Routine inhaled medications included bronchodilators and corticosteroids, nebulised antibiotics, hypertonic saline and pulmozyme.
- We do not include intravenous antibiotics, controlled drugs nor post-operative pain infusions.

Assessment

The assessment of suitability to participate is carried out on admission by the child's nurse using the self-administration tool (intranet policy appendix 5). The patient is assigned to a SAM level (see below). The decision can be made later in their stay if appropriate, and the initial assessment may also be obtained at an MDT pre-admission meeting.

Throughout the admission, the SAM level is reassessed by the nurse at the start of each shift (intranet policy appendix 6), as the patient's condition and level of supervision required may change. The pharmacist also checks the SAM level when checking the drug chart on their clinical round. If a parent/carer administering medicines is to be away from the hospital for a period of time, then the level of SAM is revised for that period.

Categories of drug administration responsibilities in the SAM scheme.

Level	Medicine administration	Medicine storage	Documenting on Medchart®
0	2 nurses	Nurse	2 nurses sign they have administered drug
1	Supervising nurse comes to patient & gives with patient/parent/carer	Nurse	Nurse signs patient on Level 1
2	Patient/parent/carer prompts nurse and give together	Nurse	Nurse signs patient on Level 2
3	Patient/parent/carer	Patient/parent/carer has access to drug locker	Nurse checks if all medication is given by patient/parent/carer and signs 'patient on Level 3'.

Other rules

- Education / information is provided by the ward pharmacy team, but outside of normal working hours the nurse provides this information.
- All medicines to be self-administered must be prescribed on Medchart. The chart is checked by the bedside nurse at regular intervals.
- The doctor should always discuss changes to the patient's medication therapy with the patient/parent/career and inform the nursing staff of prescription alterations; this must be documented.
- Patients/parents/carers are strongly encouraged to bring their current medication supplies from home.
- Medicines are stored in the Patient's Own Drug (POD) locker which has a 4-digit programmable security code that is changed for each admission. Some drugs are stored in the ward fridges (nebulised tobramycin, dornase alfa).
- PODs should be checked/assessed by the paediatric pharmacy team prior to use.

- Medicines in multi-dose compliance aids (e.g., Dosset box) may not be suitable for self-administration. Please refer to section 9.10 in the SAM policy for more information on this.

Amendments to the original policy

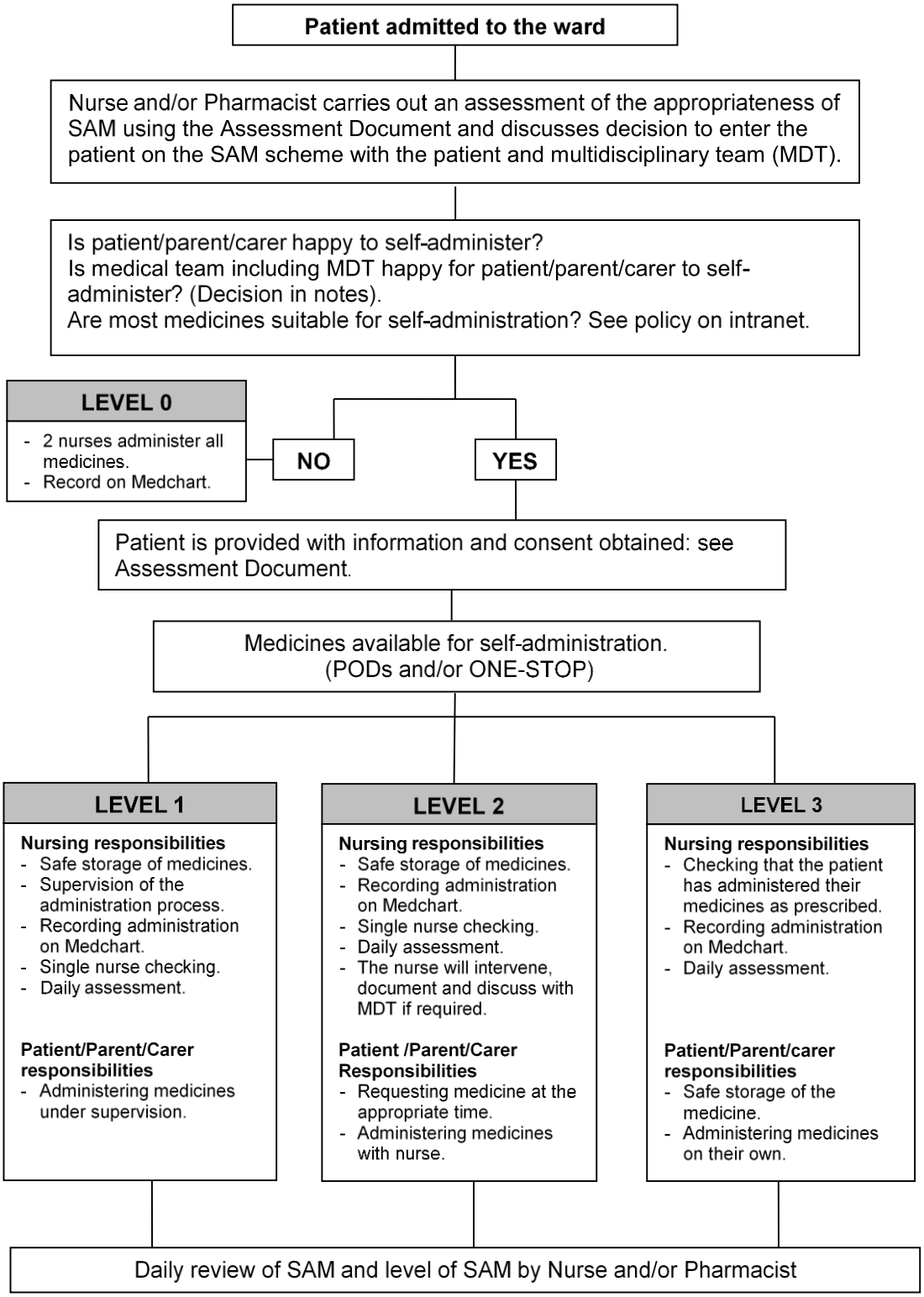
The policy has been updated because of feedback and particularly when problems were highlighted in the Datix reporting (see below).

- The drug chart was initially a standard paper chart but later became part of electronic prescribing using Medchart®.
- Parents of patients on Level 3 document drug administration on their own paper chart (intranet policy appendix 7) which is also checked by the nurse. Nurse then documents this on Medchart®.
- Children can not start the admission on Level 3 but must be on Level 2 for 24-48 hours before going on to Level 3.
- Level 3 cannot be started on a weekend.
- No PODs can be used until checked by pharmacy for condition and expiry date.

Amendments made in Nov 2021

- Level 1 can be initiated on a weekend.
- Patient/parents/carer to present with original packaging on medications if dosette box is used.
- Administration should be checked for patients self-administering at level 3 twice a shift by nurses.

SAM pathway


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

4.6 Discharge

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

- The indication(s) and general conclusions about the admission, including which IV/oral antibiotics were administered.
- Weight on admission & discharge (height on admission).
- Spirometry results (absolute and % predicted FEV_1 & FVC) on admission & discharge.
- All drugs on discharge – (*i.e.*, the medicines that patients will be expected to continue at home, including short courses).
- Ensure that you detail any changes to regular medicines and the rationale for this.
- Plan for review - when / where (this should usually by 4-6 weeks in CF clinic).
- 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 methylprednisolone).
- Whether any extra plan needs to be made for further admissions to promote success (*e.g.*, how successful invasive procedures were managed.

The summary must be completed within a few days of discharge as the children are often seen soon after admission in clinic.

A copy of the discharge should be given to the parents/young person before discharge. A copy should be filed in the patient's notes by the ward clerical staff and published onto EPR.

If any microbiology or other key results are pending, these should be added to the bottom of the ward list to chase and if urgent, should also be emailed to the CF CNS team so they are not missed.

4.7 Infection control

There are concerns about cross-infection between children with CF which dictate that certain precautions must 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 are international guidelines, and many families are anxious about cross-infection and we adhere to these views. Although our ward staff will support and reinforce these measures, we also strongly request that parents/carers help us to ensure that the children stick to the rules.

Generally, personal hygiene is emphasised, and children are encouraged to cover 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 children with chronic respiratory conditions) cups, cutlery and so forth.

The formal rules are summarised below:

1. Ward

- Each patient with CF will either be in a cubicle or in a bay with no other CF patient. No other CF patient or family member is permitted to be in another child's 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/Primary Ciliary Dyskinesia.
- We 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 inside each cubicle and each bay for use by staff, all children, families and visitors. USE THEM!
- Doctors **must** clean stethoscopes between patients. Ideally each CF patient will have a stethoscope that remains with them for the admission.
- Oxygen saturation finger probes are only used for a single patient.
- We have 7 cubicles with their own ensuite shower/toilet and a further one with its own toilet. Children may sometimes be in a bay in which case they use the shared ward bathroom/toilets. 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/bay 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 cepacian, M abscessus* complex and multiresistant *P aeruginosa* will stay inside their cubicles for the whole admission, although may spend time off the ward. Those with other forms of NTM (not abscessus) are treated the same as all CF patients.**
- When can patients be considered free of their organisms?
    - *B cepacia:* when they have **been free of the organism for 2 years, with at least 3 negative sputum or cough swabs or BAL samples per 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 on intranet (https://www.rbht.nhs.uk/sites/nhs/files/Trust%20policies/MRSA%20policy%20-%20May%202016.pdf
    - updated April 2016). 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* regarding type of respiratory sample obtained.
    - *Non-tuberculous mycobacteria:* considered eradicated when they have had **4 negative BAL or sputum samples over 1 year since their 1st negative sample**. These samples must NOT be cough swabs. 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.

2. Daily Plan

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

3. School Room

- We actively encourage attendance at our hospital school during inpatient stays for **all** patients. This not only serves to help the children to keep up with their studies but also helps them to feel as ordinary as possible during their time on Rose Ward. The hospital teaching staff are also able to look at each child's academic progress and, with the permission of the child and/or their parents to share with the wider CF team any concerns about their learning. Teaching staff attend weekly ward rounds. If permission is given from child/parent, a record of engagement with hospital school is forwarded to the child's community school on discharge.
- 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 schoolwork from the teachers that they can continue with by their bed space.
- The relevant area is cleaned between patients.

4. Playroom

- The Play Team can support children from 0-16 years.
- Rules for the playroom are similar to rules for the school rooms.
- Two children with CF can now use the area at one time (one in main room, one in smaller playroom protected by glass walls/door). 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 other CF children are having their turn in the playroom.
- Most children with CF are asked (and prefer) to eat in their cubicles/away from the ward. Occasionally when a younger child is alone in their cubicle, they will be encouraged to eat with some of the other patients (who do not have suppurative lung conditions) in the playroom.
- 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 (i.e., 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* complex
- Multi-resistant *Pseudomonas aeruginosa* (*e.g.,* Liverpool Epidemic Strain)
- Respiratory viruses *e.g.,* RSV or Influenza

Note, the above list does not include –

- *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 with regards to cross infection.
- 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 sterilised when taken out before use by another child (this includes a stethoscope). Hands are washed and rubbed with hand sanitiser before entering and leaving the room. Socialising with other patients 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,* and indeed any organism, 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) or Naseptin (neomycin and chlorhexidine) nasal ointment may eliminate MRSA 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 skin washes and mupirocin or Naseptin) 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 standard CF clinics and like all our CF patients, do not mix with other CF children in the hospital school and playroom. These patients attend clinics held on the 2nd Friday of every month. Patients with MRSA are booked into earlier time slots and those with *B cepacia* have later slots. Due to the adult *B cepacia* clinic being held downstairs, patients are advised to come in via Fulham Road entrance and go straight up the stairs and through physiotherapy into clinic.

Segregation clinics

- 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, psychologist, pharmacist) come to see him/her in that room.

- 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 should leave out-patients immediately, unless waiting for a prescription to be brought up to clinic.

- Between patients, the rooms are thoroughly cleaned (desktops, chairs, other surfaces, sinks) before 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.

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

- All children with MRSA or *B cepacia* come to clinics reserved for them only on the SECOND FRIDAY of the month with MRSA in the first wave and *Burkholderia* cepacia in the second wave. If patients are able to come back to standard clinic, they should come to the second wave of clinic.

- Children with multiresistant PsA should come to the 2nd wave of clinic.

- All children with any form of NTM come to second wave appointments only, because of the greater time (45 mins) required between patients with NTM for aerosols to disappear.

COVID-19

During the peak of the COVID-19 pandemic, we were unable to see our full quota of children face-to-face in clinic. We are seeing two waves of children in CF clinics now, although reduced numbers in the 2nd wave (as we also conduct video consultations). There is no requirement for COVID-19 testing before clinic appointments although, at the time of writing, pre-appointment questionnaires are still being completed and we request that any parent or child with a febrile illness in the 72hr period prior to their appointment does not attend for a face-to-face visit unless specifically advised to by the CNS team. With increasing access to virtual clinics, we anticipate that this will remain our position for the foreseeable future.

In terms of ward admissions this is an ever-changing situation so the Trust policy should be checked on the intranet.

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 London and South East England) in whom the diagnosis was missed by screening, or who have come from abroad where screening might not take place. About 5% of babies & infants diagnosed with CF were missed on screening in the 4-year audit. These will often have a milder phenotype, particularly regarding pancreatic status. We no longer use the term 'atypical' CF.

5.1 Newborn screening

Immunoreactive trypsinogen (IRT) is measured on a dried blood spot obtained on the Guthrie card in the first few days 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 is 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, preferably in the morning, 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 newborn screening results and that they suggest both parents may wish to be present at the visit. The Health Visitor is provided with a written prompt sheet to help facilitate the conversation (appendix 12).

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. In cases with a CFTR gene variant which is well-understood and more commonly associated with CFSPID (see below), uncertainty may be conveyed to parents rather than 'CF is likely'. At the sweat test visit, the family will be greeted by one of the CF nurse specialists, and whenever possible, seen briefly by the consultant, to introduce themselves. The sweat test (in duplicate) is performed, which is mandatory, (even if two genes have been identified), to rule out any the remote possibility that the screening sample has been misidentified. Results are available within an hour, allowing, in the majority of cases, the diagnosis to be confirmed to the family by the Consultant; in rarer cases where the diagnosis is unclear, we follow a different pathway - see below. The Consultant will then take a full history, carry out an 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 CF Education Visit. In general, currently, screened babies are well.

Treatment will usually not be initiated at this time except for pancreatic enzyme supplements if symptoms are indicative of pancreatic insufficiency (abnormal stools, very hungry baby, concerns overweight, classic genotype); if there is doubt the dietitian will see the baby that day. A sample will be collected for stool elastase or parents are given a pot to send back. Very occasionally oral antibiotics may be started if the baby has chest symptoms; a cough swab should be obtained in these cases.

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.

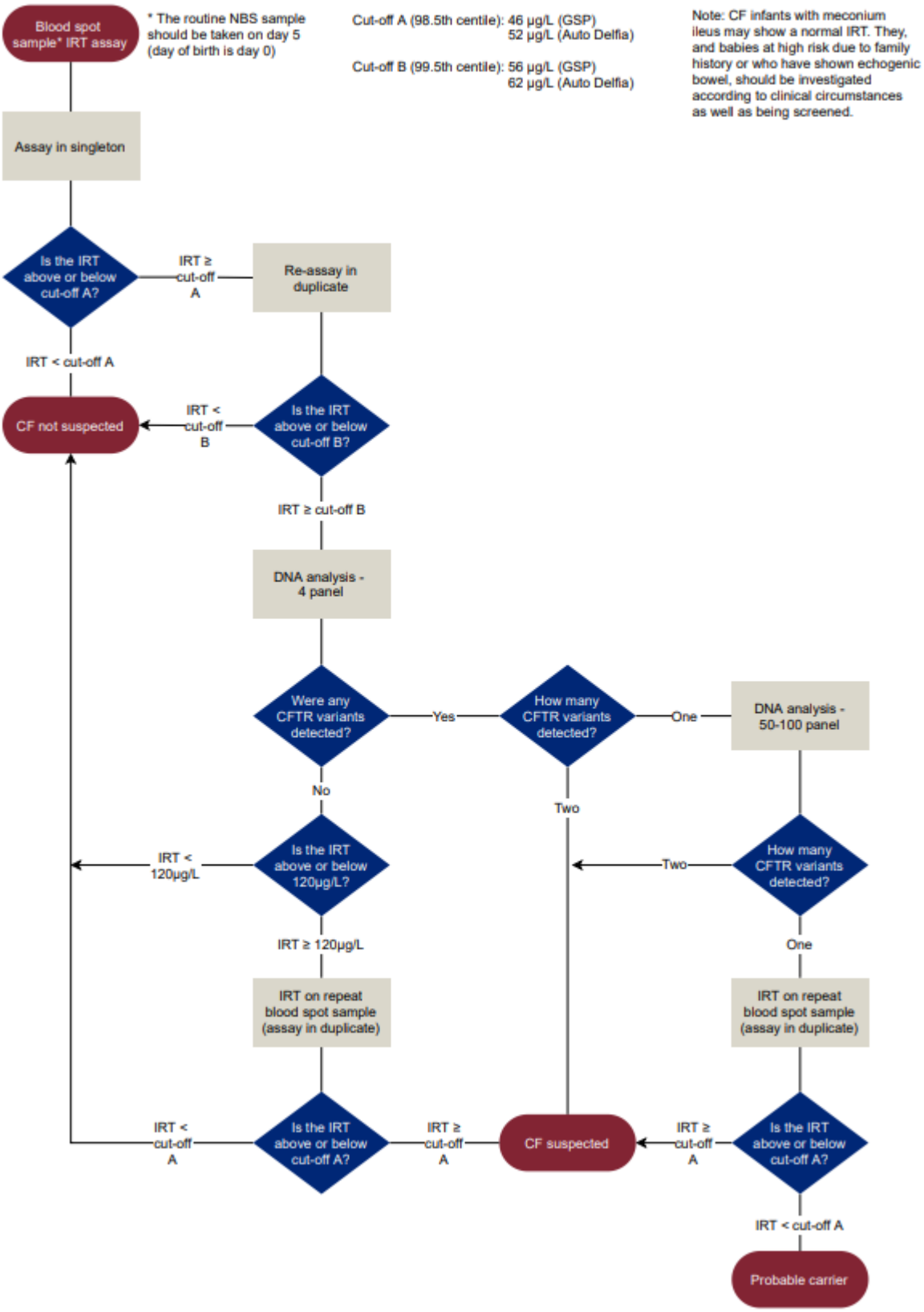
A one-day education programme is arranged for the following week; this usually takes place in the paediatric outpatient department. The programme involves a prearranged timetable to ensure that each member of the MDT has an allocated slot in which to teach the family about their role within CF. They will meet with the consultant, nurse specialist, dietician, physiotherapist, psychologist, and pharmacist or paediatric pharmacy technician. An education visit is also done for older patients being transferred into our unit from abroad or other CF centres.

Medication and physiotherapy are started during the education visit.

After the education visit, the home care nurse visits the family the next week to offer support and go over what the parents were taught. 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 education visit.

We no longer routinely do a sweat test on older siblings of babies diagnosed by screening, unless there is a clinical need as the child is symptomatic, or if the parents are concerned.

Below is the UK screening algorithm, updated January 2021. Available in full on https://www.gov.uk/government/publications/cystic-fibrosis-screening-laboratory-handbook/cystic-fibrosis-screening-laboratory-handbook#:~:text=screening%20programme%20guidance.-,Screening%20for%20CF,initiation%20of%20high%2Dquality%20care.


Blood spot sample* IRT assay
* The routine NBS sample should be taken on day 5 (day of birth is day 0)
Cut-off A (98.5th centile): 46 µg/L (GSP) 52 µg/L (Auto Delfia)
Cut-off B (99.5th centile): 56 µg/L (GSP) 62 µg/L (Auto Delfia)
Note: CF infants with meconium ileus may show a normal IRT. They, and babies at high risk due to family history or who have shown echogenic bowel, should be investigated according to clinical circumstances as well as being screened.
Assay in singleton
Is the IRT above or below cut-off A?
IRT ≥ cut-off A
Re-assay in duplicate
IRT < cut-off A
CF not suspected
IRT < cut-off B
Is the IRT above or below cut-off B?
IRT ≥ cut-off B
DNA analysis - 4 panel
Were any CFTR variants detected?
Yes
How many CFTR variants detected?
One
DNA analysis - 50-100 panel
No
Two
IRT < 120µg/L
Is the IRT above or below 120µg/L?
Two
How many CFTR variants detected?
IRT ≥ 120µg/L
One
IRT on repeat blood spot sample (assay in duplicate)
IRT on repeat blood spot sample (assay in duplicate)
IRT < cut-off A
Is the IRT above or below cut-off A?
IRT ≥ cut-off A
CF suspected
IRT ≥ cut-off A
Is the IRT above or below cut-off A?
IRT < cut-off A
Probable carrier

5.2 Clinical presentation

This is rare now that newborn screening is well established. However, it is **essential** that the possibility of a CF diagnosis is not ignored or 'ruled out' in a screened baby as false negative screen failures do occur. Additionally, children born before screening may present late with clinical features, as may those born abroad. Lack of experience of clinical staff may 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 faltering growth 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 neonatal 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) most children in whom CF needs to be excluded will undergo sweat testing. This group will include the following:

- Baby with a positive newborn screen.
- Child with suggestive history / symptoms/ examination.
- Sibling of a newborn screened infant – we only do this if there is clinical suspicion or if the parents wish us to due to their need for reassurance.
- 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 diagnostic 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 updated in 2014 – file:///C:/Users/IB963/Downloads/Guidelines-for-the-Performance-of-the-Sweat-Test-for-the-Investigation-of-Cystic-Fibrosis.pdf

Results must be interpreted in the clinical context

Normal range Cl^- <30 mmol/l;
Borderline Cl^- 30 to 60 mmol/l
(although may still be CF; diagnosis can be confirmed if 2 disease-causing CFTR variants, or an abnormal advanced test e.g., nasal potential difference).
CF confirmed Cl^- >60 mmol/l.

Chloride is the ion measured. We do not measure conductivity and the available evidence does not in our opinion advocate its use. The diagnosis of CF should be made based on 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, commonly listed in old texts as a cause of false positive sweat tests, 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. Discuss the case and the possibility of 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 2000 identified variants in the *CFTR* gene, although not all of them are associated with the clinical picture of CF. Mutations fall into different classes (I-VII), with commonest in the Caucasian population being a class II mutation, F508del (formerly) ΔF508. Nomenclature has changed (see appendix 13).

The CFTR2 website is a growing resource which provides excellent data on gene mutations and their expected effects. See www.cftr2.org.

In all children with a diagnosis of CF, we seek to fully identify two gene mutations including by full gene sequencing if required because:

- Is an eligibility criterion for mutation-specific therapy (e.g., ivacaftor and Kaftrio) and may allow enrolment into clinical trials of other agents.
- In a child diagnosed with CF:
    - it facilitates screening for other family members.
    - and allows prenatal diagnosis of future pregnancies.
- For pregnant women who already have an affected child with CF and have not undergone antenatal testing, the status of the new infant may be confirmed more quickly if cord blood is sent for genetic testing, than waiting for results of the screening programme. In the case of rarer genotypes associated with residual CFTR function, it also reduces the chance of a false negative screen. This should be offered, and if parents are keen, they should be provided with a genetic test request form and blood bottle. Cord blood is not recommended routinely for siblings of children with CFSPID designation (see later). If positive on genetics, this must be followed up by a sweat test (as with all NBS babies who are positive), and if sweat not obtainable, the baby must have the genetics repeated. This is to ensure cord blood is not contaminated with maternal blood.
- 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).

- We will also use extensive genotyping (including introns) in cases of borderline diagnosis.

Based on current knowledge, genotype analysis should *not* be used to guide prognosis in an individual child. Pancreatic status should be confirmed with a faecal elastase in all cases; PS may evolve into PI over time, so repeat measurements should be considered, and attention paid to symptoms and nutritional progress.

Limitations of variant analysis

The term 'genetic variant' is now preferred to 'mutation'. Due to the large number of identified genetic variants (>2,000 although not all confirmed as truly disease-causing), and the extreme rarity of many of these, it is only practical to screen for a few on a routine basis. The first-line screen currently includes the commonest 50. Clearly therefore failure to detect variants does not exclude the diagnosis. This is particularly true in a child of non-Caucasian origin. There is now a specific panel of gene variants, 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 variants can be looked for. Full gene sequencing can be performed if specifically requested but is expensive (in the order of £500) and time-consuming; whilst previously we would not have performed this routinely in patients with a clear-cut biochemical diagnosis, all children should now have a genetic cause actively pursued as they may be eligible (now or in the future) for small molecule modulator therapies or trials of these drugs. Samples for both first-line screen or full sequencing should be sent to the Clinical Genetics Lab in house at the Royal Brompton using the genetic testing form available on the intranet. Note - these forms require parental signature to indicate consent. The lab will also perform non-CFTR ion channelopathy testing in complex cases; please contact Prof Jane Davies to discuss any such cases.

5.5 CF Screen-Positive, Inconclusive Diagnosis (CFSPID)

There are two scenarios in which making a diagnosis after a positive NBS is less easy:

1) Borderline sweat test (30-60 mmol/L) in the absence of two *disease causing* gene variants. *
2) Normal sweat test in the presence of 2 CFTR variants, at least one of which is of uncertain significance.

In both these cases, the 'significance' of gene variants can be looked up on the CFTR2 website on ww.cftr2.org, which categorises them into 'disease-causing', 'variable clinical consequence (VCC; see below)' and 'non-disease causing'. The website currently covers the commonest variants, although the database is growing with time.

* This changed in our 2020 guideline vs our older guidelines based on a Delphi consensus process (*J Cyst Fibros 2015;14:706-13*) in which a borderline sweat test (30-60 mmol/L) with two CFTR variants would not be classified as CFSPID, even if one or both of these were VCC. The more recent consensus diagnostic guidelines (Farrell PM et al. J *Pediatr*. 2017;181S:S33-S44) now state that in the absence of two *disease-causing* variants, a

positive (≥60 mmol/L) sweat chloride is required for a CF diagnosis. The main group affected by this change is babies with F508del/ R117H-7T (or another VCC) with intermediate sweat Cl-, who were previously regarded as CF but should now be labelled as CFSPID. Babies with <2 CFTR gene variants identified should have full *CFTR* sequencing *without delay.*

It is essential that the diagnostic uncertainty is shared with the parents and we avoid any temptation to 'label' a baby prematurely; undoing a CF diagnosis poses its own problems for families.

Genotypes of varying clinical consequence (VCC)

- There are a number of mutations in this category. Most common one leading to this scenario is R117H-7T (if R117H is reported, it is *essential* the 7T/5T variant is included, otherwise check with lab).
    - R117H-**5T** leads to low levels of CFTR function and is considered a CF disease-causing mutation.
    - R117H-**7T** leads to variable amounts of CFTR function and is so commonly found in non-CF populations in combination with F508del, that this is not considered diagnostic. Some patients with these mutations will have CF, usually pancreatic sufficient and often presenting with symptoms much later in life, but most will not. Some will be detected through screening and designated CFSPID, but we know from population studies, that most will not be picked up at all.
    - **9T** is very rarely 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 CF-causing R117H-5T mutation.
- Other mutations in this category (this not comprehensive, so if in doubt, check CFTR2): D1152H, L997F, 5T.

Follow up

All CFSPID babies should be referred to Prof Jane Davies' general respiratory clinic, where they will receive further information, clinical surveillance and further CFTR functional testing (repeated sweat testing, stool elastase) and low level clinical monitoring until the clinical picture becomes clearer.

The possibility of male infertility related to CBAVD (congenital bilateral absence of vas deferens) is always discussed; the vas deferens is the most sensitive organ in the body to loss of CFTR function and CBAVD will be present in a proportion of cases.

The main aim is to avoid over-medicalisation, whilst maintaining sufficient observation of the baby to detect any concerns. CFSPID is not a diagnosis, nor was it intended for long-term use; it should rather be regarded as a holding label. We seek clarification over time of the clinical status:

(1) Evolve into CF:

- increasing sweat Cl- into diagnostic range.
- 2 disease-causing CFTR variants recognised on subsequent genetic testing of a child with a previously incomplete genotype, or because of updates to the CFTR2 website.
- evolution of clinical symptoms –

    - development of pancreatic insufficiency would be enough but is very rare in this group.
    - respiratory symptoms can be more difficult, as all young children get coughs. Severe or persistent symptoms would be of concern, as might those accompanied by positive cultures such as *P. aeruginosa.* It is important not to overlook alternative explanations for respiratory symptoms in this group, as we have diagnosed, for example, unsafe swallow, atopic asthma etc.
- CFTR dysfunction confirmed on nasal PD (although this is very difficult in young children and will only be undertaken in cases of high clinical suspicion).

After MDT discussion, children evolving into any of the above groups may be transitioned into the CF clinic and will then be entered onto the national CF registry; they may continue to have a milder clinical course than their conventionally diagnosed counterparts. The parents will be invited to come for our standard education visit for newly diagnosed children.

(2) Remain well with normal or borderline tests (vast majority of CFSPID babies are in this category):

- We review babies every 6-12 months in a general respiratory clinic, tailored to clinical need and parental anxiety.
- There is a lack of consensus throughout Europe on whether to routinely culture airway secretions in this group; in our clinic, we are undertaking symptom-guided and NOT routine cough swabs.
- We are considering how best to undertake long term care of these children. It is likely that we may see them with decreasing frequency and/ or transition to telephone follow up during childhood.
    - Consider sensitive pulmonary tests currently *e.g.*, LCI as a benchmark.
    - Ask the family to alert us early of any clinical concerns, particularly chest problems.
    - Review in person when the child reaches adolescence:
        - Consider lung function testing and LCI.
        - Discuss the risk that some of these patients may acquire chest disease (sometimes significant bronchiectasis) in adulthood, importance of smoking avoidance etc. will be discussed.
        - Revisit the issue of infertility in a male CFSPID case.
        - Recent published advice mentions CT chest scanning. In our clinic, given our expertise in LCI, we only do a CT scan if an LCI is abnormal.
- Jackie Francis is the CFSPID nursing link, through whom any enquires can be passed.
- Michele Puckey, Consultant Paediatric Psychologist, has an interest in this field and can be consulted for help; these parents often find the uncertainty extremely difficult to deal with.
- At the current time, these babies should not be entered onto the national CF registry, although work is in place to adapt the registry to include a specific CFSPID section. Should they acquire a diagnosis of CF later, they will be added then.

5.6 Antenatal testing

Carrier parents contemplating another pregnancy should be referred for genetic counselling 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).

Based on 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 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 ask their GP to refer them to their local genetics centre who will then refer on to Guy's and St Thomas' Hospital Centre for Preimplantation Genetic Diagnosis. https://www.guysandstthomas.nhs.uk/our-services/pgd/about-us/welcome.aspx. Guy's and St Thomas' will not take direct referrals, they must all come via local genetic centre.

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 their web address above 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 Biochemistry Department of Sandwell and West Birmingham City Hospital.

- **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 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. We are not currently undertaking this in the CFSPID population but will consider it when a clinical concern arises. Please refer to Prof Jane Davies (via PA, Gina Rivellini, g.rivellini@imperial.ac.uk, 0207 594 7986), who runs a specialised nasal PD clinic approximately every 2 months, mostly for external referrals.

5.9 Routine investigations for newly diagnosed patients

For many years we have carried out routine surveillance bronchoscopy and pH study on all newborn screened infants at 3 months of age. Our latest audit of data no longer supports use of routine bronchoscopy over surveillance swabs, which has been aided by the introduction of induced sputum cultures. We are also aware that it is quite difficult for the families to have their baby undergo this general anaesthetic procedure. We will certainly have a low threshold though for diagnostic bronchoscopy and BAL in young children if there is any clinical concern, and induced sputum has not been helpful.

Our data has revealed 50% infants have gastro-oesophageal reflux. We will continue to have a low threshold for starting reflux therapy when babies have symptoms. Furthermore, if infants have recurrent growths of coliforms (*e.g.*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Citrobacter*), we will assume the child has reflux, treat accordingly and consider a pH study.

Blood is taken if the CF genotype is not known from the heelprick screening sample, although the laboratory may have stored DNA if extended genotyping is required so check first. Otherwise, blood is not taken until 1st annual review.

Respiratory care

6.1 Chest exacerbation

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, and greater likelihood of progression to transplantation or death. 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 outpatients 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, even when a doctor says the 'chest is clear'.
- 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 (including if the local hospital is involved), it is essential that the CF nurse specialist is informed, so appropriate follow up (home care team, telephone, out-patient clinic) 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) should be given before resorting to IV antibiotics. Some children need IV antibiotics from the start.

The published literature shows that virtually all improvement in spirometry occurs by day 13, and if there is no improvement by day 7, this is an adverse prognostic sign. We therefore need to formally reassess progress on **day 6-9**, and if there is no improvement in spirometry

consider (a) induced sputum or bronchoscopy to determine if there is an untreated infection; (b) additional mucolytics; (c) change in IV antibiotics; (d) consideration of another diagnosis, *e.g*., ABPA, reflux and aspiration; (e) non-CF associated coincident diagnosis; (f) ensure child is well hydrated.

New data (STOP-2 study) on duration of IV antibiotic treatment in adults shows that if there is early improvement then 10 days treatment is non-inferior to 14 days. If initial response is poor, 14- and 21-days treatment are equivalent. Default remains 14 days in children but shortening the course (10 days) can be considered (Consultant decision).

IV antibiotic courses may be extended to a third week because of symptoms or to increase time to next relapse, but spirometry is unlikely to improve. Multiple pulmonary exacerbations should lead to consideration of discussion in the CF Focus meeting. A crude adherence check (prescription uptake and downloading data from their nebuliser) should be considered as part of the evaluation of an exacerbation.

6.2 Antibiotics

6.2a Policies & specific organisms

6.2a 1. Introduction – some principles

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 for some antibiotics, and to ensure high levels of tissue and sputum penetration (see drug formulary section 11). CF is a serious condition, and the aim of therapy is to push antibiotic doses to the upper therapeutic range. 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. 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). There is no evidence that *in vitro* sensitivity testing correlates with clinical outcomes.

6.2a 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. Use treatment dose of co-amoxiclav for minimum of 2 weeks.

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 (particularly for *S.aureus*) is a concern. We do not tend to use oral cephalosporins although the concern with *P aeruginosa* relates more to their prophylactic use. Note that cefixime has no anti-staphylococcal activity and should not be used in this context.

iv. Oral ciprofloxacin for **2-3 weeks** if no recent course, 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.

v. 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.

vi. 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. Remember a normal child with a normal cold may have symptoms for 3 weeks, and 10 colds a year is normal in a pre-school child.

6.2a 3. Surveillance respiratory cultures

Cough swabs/sputum must be sent every time a child is seen in clinic, on the ward or as indicated at a home visit. All sputum requests must be sent for microscopy culture, sensitivity, fungal and non-tuberculous mycobacteria. 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. We may encourage patients to bring in recent sputum specimens from home if attending clinic on that day (as may be more productive with morning airway clearance session).

In some circumstances parents may be advised to take a cough swab at home following discussion with the Clinical Nurse Specialist (who will establish that a medical / homecare review is not immediately indicated). However, this should only be in the presence of symptoms, in children who can cough to command and following appropriate training for parents /carers.

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.

6.2a 4. Treatment of an exacerbation when the organism is unknown (blind therapy)

- 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. Generally though 2 weeks is sufficient.
- Consider oral azithromycin 10 days.
- Consider oral ciprofloxacin 14 days 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. Our CF nursing team though will take the initiative and speak to the parents anyway.
- If spirometry was reduced at diagnosis, it must be repeated (in clinic or at home).

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, especially if colistin-resistance is reported (see appendix 20 for contact details).

6.2a 5. Intravenous antibiotics – principles for <u>unknown</u> organism

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

We are reducing our use of IV aminoglycosides and will limit them to when *P aeruginosa* or other gram negative organisms are a confirmed issue.

New data shows that children who are *P aeruginosa* free for a year or more did equally well with *P aeruginosa* and non-P aeruginosa regimens; discuss with Consultant if you think a non-P aeruginosa regimen is appropriate. Remember that nebulised antibiotics may suppress *P aeruginosa*, so always discuss an apparently negative patient on nebulised antibiotics with a Consultant.

We are reducing our use of IV meropenem and instead using IV cefuroxime when no organisms have been isolated. **An induced sputum should be carried out at the start of the course in a non-sputum producer with no recent bacterial isolation, we do not just rely on a cough swab.**

Never had *P aeruginosa*	IV cefuroxime single agent.
No *P aeruginosa* for 3 years (must include last year off nebulised antibiotics)	IV cefuroxime single agent.
Chronic *P aeruginosa* infection, including those still on nebulised antibiotics *	IV ceftazidime and tobramycin
Recently isolated organisms	See relevant sections below.

- *Chronic infection with P aeruginosa* – ceftazidime & tobramycin is 1st line unless previous sensitivities or patient experience that another combination works better, suggest otherwise.
- We no longer start teicoplanin routinely if *S aureus* has been isolated within the last year.

In those with no positive cough swab (non-sputum producing children) we will carry out induced sputum or NPA with hypertonic saline at the start of the admission.

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).

6.2a 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 a pathogenic organism is always treated. We may repeat cultures before deciding whether to treat an unusual organism, especially if its pathogenicity is uncertain.

6.2a 6 I. *Staphylococcus aureus*

Ia. Prophylaxis

- The question of staphylococcal prophylaxis is based on a few studies only and evidence for benefit is weak. We have been part of the CF START national study (www.cfstart.org.uk/) on the role of flucloxacillin prophylaxis, and recruitment finishes soon. We will wait for the results of the study, but in the meanwhile continue our standard practice of using flucloxacillin prophylaxis.

- Some babies really will not take flucloxacillin, so try another brand if available. We no longer switch to co-amoxiclav. 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* rapidly becomes macrolide resistant. See formulary section 11.1a for doses

- Once aged 3 years, flucloxacillin 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 possible, for treatment) because of evidence implicating this class of antibiotics as causing a greater prevalence of infection with mucoid *P aeruginosa.*

Ib. Exacerbations

- Whether on flucloxacillin prophylaxis or not, give treatment dose for **2 weeks** if *S aureus* is isolated and thought to be cause of the exacerbation. This dosing is not affected by CF START. This will likely be with flucloxacillin or co-amoxiclav.
- Check cultures 2 weeks after finishing the 2 week course.
- If need IV antibiotics for *S aureus*, use IV meropenem + tobramycin, for 2 weeks, with IV teicoplanin just in the 2nd week if grow SA despite the 1st line IVABs. Flucloxacillin is not used IV as it causes problems with IV lines and may cause backache.

Ic. First isolation

- *In a well child* (clinical judgment) receiving flucloxacillin prophylaxis, we use oral co-amoxiclav for **2 weeks**.
- *In a well child* (clinical judgment) **not** receiving flucloxacillin prophylaxis, we use oral flucloxacillin for **2 weeks**.
- Check cultures 2 weeks after finishing the 2 week course.
- *In an unwell child* admit for IVABs. Use Meropenem + Tobramycin for 2 weeks, with IV teicoplanin only if still growing *S aureus* despite the IVABs.
- It has been shown that *S aureus* are present on toothbrushes, so we recommend replacing toothbrushes and electric toothbrush heads after eradication therapy, as they are a potential source of reinfection.

Id. Re-growths

- *Re-growth less than 6 months* from 1st growth - oral flucloxacillin for **2 weeks**.
- *Re-growth after more than 6 months* from 1st growth - treat as for 1st growth (see above).
- *Further re-growth within 6 months* – Our 2nd line is now linezolid for **10 days** as we are avoiding rifampicin in those on CFTR modulators. We will still use rifampicin and fusidic acid in those not on CFTR modulators for **2 weeks**.
- Check cultures 2 weeks after finishing the antibiotic course.
- Also consider skin decontamination using MRSA protocol.

Ie. Chronic infection

- If there are more than 2 isolates of *S aureus* in a year, give prophylaxis with flucloxacillin as above (remember under 3s may be on flucloxacillin anyway).
- Check adherence to flucloxacillin prophylaxis.
- Consider stopping prophylaxis in older children if no growth for 2 years.
- For those repeatedly culturing *S aureus* despite regular high dose flucloxacillin, consider other treatments, especially in older children. This may take the form of a different prophylactic agent *e.g.*, doxycycline in older children (with adult dentition), or nebulised vancomycin.
- The other tactic is more aggressive intermittent treatment for eradication *e.g.*, doxycycline in children with adult dentition, co-amoxiclav, fusidic acid and rifampicin (in combination), co-trimoxazole, or linezolid.
- Also consider skin decontamination using MRSA decolonisation protocol (look up MRSA decolonisation protocol on hospital intranet).
- We are going to add azithromycin on sensitivity testing, to ensure no resistant *S.aureus* present in those on long term azithromycin.

6.2a 6 II. *Haemophilus influenzae*

IIa. First isolation

- *In a relatively well child* (clinical judgment) we use oral co-amoxiclav for **2 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.

- *In an unwell child* admit for IVABs. It is most unusual for someone with CF to require IV antibiotics just from *H influenzae*. So we would probably end up with broader spectrum *e.g.* ceftazidime + co-amoxiclav.

IIb. Re-growths

- *Regrowth less than 6 months* from 1st growth - oral co-amoxiclav for **2 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

- This is most uncommon. 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.

6.2a 6 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 20 for contact details).

Antibiotic sensitivity for PsA isolates is not done more often than every month. VNTR typing is done on new PsA growths *i.e.*, 1st growth or if not previously isolated for 1 year. It is sent automatically by the Microbiology Lab.

IIIa. First isolation

- If grown on cough swab, we carry out eradication -
  - **3 weeks** oral ciprofloxacin (or dual therapy intravenous antibiotics if unwell)
  - PLUS **1 month** nebulised **tobramycin** twice daily.
- If the child is unwell or young (under 1 year) we may decide to use IV antibiotics.

- If the 1st growth is **mucoid** *P aeruginosa*, we use ciprofloxacin for 3 weeks plus **3 months** nebulised therapy (tobramycin/colistin/tobramycin).

- 10-20% fail the 1st attempt at eradication. Warn the parents in advance to reduce later disappointment.

- After eradication therapy for new *P aeruginosa*, patients will all have an induced or spontaneous sputum culture checked at 1-2 weeks after finish tobramycin to see if eradication has been successful.

- If they remain symptomatic and sputum culture was negative, they will have an induced sputum or BAL. We will not rely on a cough swab to prove successful eradication.

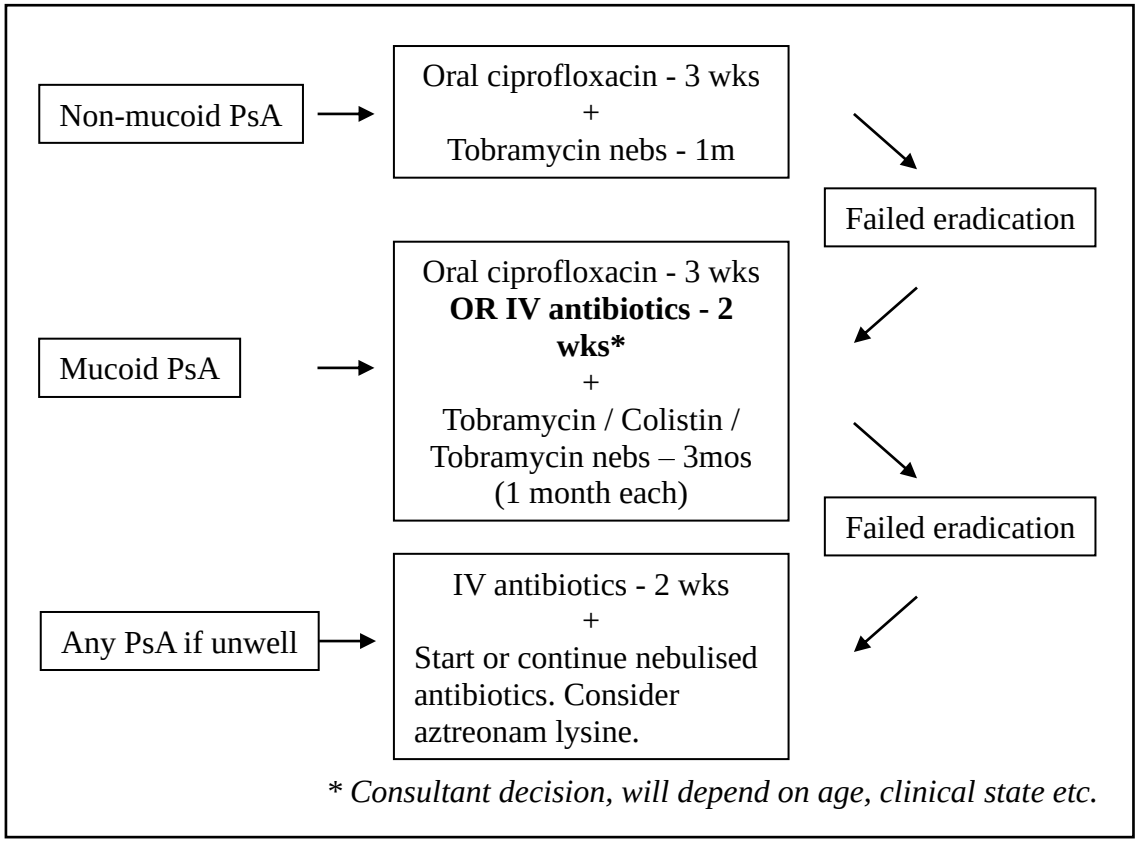
- It has been shown that *P aeruginosa* bacteria and biofilms are present on toothbrushes, so we recommend replacing toothbrushes and electric toothbrush heads after eradication therapy, as they are a potential source of reinfection.

IIIb. Failed eradication

- Treatment is given on a case by case basis.

- If the child is well, give another 3 weeks oral ciprofloxacin. If ciprofloxacin-resistant, check sensitivities and consider *e.g.*, chloramphenicol. Also give a further 3 months nebulised therapy. This will be 1 month tobramycin – 1 month colistin – 1 month tobramycin.

- If eradication has failed again (after the 3 months nebulised treatment), we will give IV ceftazidime + tobramycin. We will also consider nebulised aztreonam.



IIIc. 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 plus 1 month nebulised tobramycin.

- 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).
- **Long term nebulised antibiotics** –
    - If the regrowth occurred within the year of eradication therapy, after re-eradication, we use long term nebulised antibiotics. This is usually colistin.
    - If regrowth happened after a longer gap, over 1 year, after re-eradication we do not necessarily start long term nebulised antibiotics.
    - If they were on colistin when they had the regrowth, consider switching to nebulised tobramycin alternating monthly with colistin.
    - If they had regrowths despite alternating colistin/tobramycin, consider nebulised Aztreonam lysine (Cayston) as 3rd line for 1 month (Consultant decision). This may need to continue alternating monthly with colistin or tobramycin.
    - If there have been no *P aeruginosa* growths for 2 years, consider whether long term antibiotics can be stopped.

IIId. 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, (see formulary). We rarely use piptazobactam because of allergy including cross reactions.
- If a child is receiving 3 monthly IV antibiotics, we will only use an aminoglycoside for alternate courses.
- Intravenous fosfomycin is a *Consultant decision* only, for very resistant *PsA*.
- We never use IV gentamicin (it is not in our formulary).
- Check whether patient allowed aminoglycosides (known renal, hearing problems).

IIIe. 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, less nephrotoxicity, and data suggesting that *P aeruginosa* is more often resistant to gentamicin than tobramycin.

Note that ototoxicity is a proven side-effect of aminoglycosides, in particular amikacin, and **all parents/carers/children** should be warned about this and be asked to sign a consent form having been offered the information sheet **every time** any aminoglycoside course is prescribed.

Audiometry should be performed:

- as a baseline at the start of commencing treatment for NTM (IV amikacin) and repeated after1 year.
- in all children starting on regular 3 monthly IV antibiotics and will be repeated yearly.
- if a child ever has a high aminoglycoside trough level.

Audiology should be arranged by referral to the child's local audiology clinic.

If any hearing deficit is detected or tinnitus is reported then consideration of stopping aminoglycoside therapy and switching to alternative treatments should be made. Tinnitus during IV administration should make you wonder if the line has become displaced up the jugular vein.

N-acetylcysteine. A systematic review has shown that the antioxidant N-acetylcysteine (NAC) has a protective effect against aminoglycoside-induced hearing loss, reducing the risk of ototoxicity by 80%.

- We use oral N-acetylcysteine at the time of IV aminoglycoside therapy for **all** courses in all children.
- See formulary 11.1g.

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 (max 660 mg)
Amikacin	30 mg/kg once daily over 30 minutes (max 1.5 gms)

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. Note that false positive high levels have been reported from blood samples taken from a finger contaminated with the antibiotic.
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. 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).
e) If the patient's renal function remains unchanged throughout the remaining course continue the reduced dose and recheck the level weekly thereafter.
f) Peak levels are not done routinely but may be taken if there is concern about clinical progress. This should be taken 30 minutes after the end of the infusion. Discuss with the Paediatric Pharmacy Team regarding what peak levels to aim for.
g) Each time levels are done, document in the notes and on EPR; the next dose is withheld until this is done (nurses will not give it until see results on EPR):
Date/time blood taken
Dosage regimen
Results
Any change to dosage
Any other action taken

Consider measuring aminoglycoside trough levels more frequently if –

- Dehydration
- Intercurrent diarrhoea and/or vomiting
- DIOS
- Other nephrotoxic drugs *e.g.*, ibuprofen.

IIIf. Chronic *P aeruginosa* infection

See NHSE Clinical Commissioning Policy for inhaled therapy first published Dec 2014.
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf

- **Chronic *P aeruginosa* infection 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 *P aeruginosa* with significant chest symptoms and declining lung function, 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. *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. It is not commissioned by NHSE for continuous use (*i.e.*, every month) but only for alternate month use.

- We use nebulised aztreonam **TWICE DAILY**, and only suggest three times a day for particularly troublesome cases.

- A stepwise approach is recommended, colistin remains 1st line, alternating tobramycin/colistin remains 2nd line treatment. Aztreonam is our 3rd line alternating with colistin. **Consultant decision**. Nebulised levofloxacin is not licensed for <18 years.

- 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 (saturation studies and auscultation for young children who cannot do spirometry). If bronchoconstriction occurs, use pre-dosing with a bronchodilator, and repeat the supervised challenge. Nebulised salbutamol can be added to colistin (but **not** tobramycin or aztreonam). Otherwise, inhaled salbutamol should be given beforehand via a spacer. See section 6.16c.

- **Long term intravenous colistin**. We have not needed to use this for many years.

IIIg. Dry powder antibiotic inhalers (see also section 6.16e).

- 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 ICE and the request form which is on intranet). It is essential to check the child knows how to use the device, as with all inhaled medication.

- **TOBI Podhaler**
  Tobramycin given by the TOBI podhaler has been shown to be non-inferior to TOBI. 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. The first month will be prescribed in clinic and supplied by our pharmacy; subsequently it will be supplied by the hospital's homecare provider.

- **Colobreathe turbospin**
  Colobreathe to deliver colistin has been shown to be equivalent in efficacy to nebulised TOBI. The current clinical commissioning policy for Inhaled Therapy for CF states that as per NICE guidance, this can be used for patients who have previously been prescribed colistin nebulised treatment and would continue to benefit from treatment but have otherwise become intolerant or have struggled to adhere with nebulised treatment and therefore would be switched to a more expensive product such as tobramycin nebules. The first month will be prescribed in clinic and supplied by our pharmacy; subsequently it will be supplied by the hospital's home care provider.

6.2a 6 IV. MRSA

- At least 3 trials of MRSA eradication have successfully used oral trimethoprim and sulfamethoxazole (co-trimoxazole) combined with rifampicin for either 14 or 21 days.
- Topical treatment was either nasal, skin and oral decontamination and a three-week environmental decontamination, or five days intranasal mupirocin. Therefore for 1st isolation in sputum/cough swab, we attempt eradication as there are data showing MRSA adversely effects lung function.
- If on CFTR modulators, 1st line is **linezolid for 2 weeks**. Consider co-trimoxazole, depending on sensitivity. If not on Kaftrio etc. we will still use **rifampicin and co-trimoxazole for 2 weeks.** 2nd line alternatives - fusidic acid or trimethoprim added to rifampicin. Beware of hepatic toxicity.
- Prophylactic flucloxacillin should not be used in patients with MRSA for 2 years after MRSA is cleared, but flucloxacillin can be used as treatment for subsequent MSSA growths.
- Use of long term azithromycin is not affected.
- Nebulised vancomycin can also be considered (see formulary).
- Vancomycin and teicoplanin are IV drugs active against MRSA. Teicoplanin does not generally 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.
- Check current hospital policy on the intranet; also remember surface decontamination protocols. Ensure whole family undergoes decontamination (their GP will need to prescribe this) with for example chlorhexidine mouth washes, nasal mupirocin and chlorhexidine body wipes.

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 can cause blood dyscrasias and the risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than our younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy. There are also reports of optic neuropathy with courses >28 days. If the child has significant nausea, consider venous blood lactate measurement as the drug can cause lactic acidosis.

Therefore, linezolid should only be started on consultant approval and we will aim for 10 day courses. We will NOT take blood for FBC if course is < 14 days, but if on it for 14d or more, then FBC must be monitored weekly. For those on prolonged (4 weeks or more) or repeated courses, ophthalmological assessment is mandatory and should be repeated every TWO months. Also consider use of high dose pyridoxine (vitamin B_6 100mg od) to reduce risk of cytopenias for prolonged courses. Where possible patients should be warned to immediately report any visual changes, regardless of treatment duration.

6.2a 6 V. *Burkholderia cepacia* complex

The *Burkholderia cepacia* complex consists of many well-established genomic species called genomovars: some examples are *B. cepacia*, *B. multivorans*, *B. cenocepacia*, *B. vietnamiensis*, *B. stabilis*, *B. ambifaria*, *B. dolosa*, *B. anthina*, *B. pyrrocinia* and *B. pseudomultivorans*. 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 criterion 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 20 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. Whilst waiting for the confirmation, it may be appropriate to start some therapy as even if not *Burkholderia*, it will be some type of gram negative bacteria *e.g.*, *Pseudomonas* spp.

- 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. 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, 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.

6.2a 6 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. However, if not responded to cotrimoxazole, sensitivity testing can be requested and may be helpful. Can also use a 2-4 week course of chloramphenicol (currently a very expensive option in UK), or trimethoprim, or minocycline if >12 years old (>8 years if adult dentition confirmed by a dentist). Doxycycline may be used as an alternative as it is once daily – sensitivity to minocycline should imply sensitivity to doxycycline. If the child meets criteria for a pulmonary exacerbation, and *S maltophilia* is the only organism isolated, consider high dose intravenous co-trimoxazole (*Pneumocystis jiroveci* treatment dose, Consultant decision). It may be necessary to start at a lower dose and work up.

6.2a 6 VII. Non-tuberculous mycobacteria (NTM)

Background

Nontuberculous mycobacteria (NTM) or atypical mycobacteria are environmental organisms with relatively low virulence, found in soil and water that are potential pulmonary pathogens increasingly affecting patients with CF. There are many species and the commonest to affect the lungs are:

• *M avium* complex (MAC) which includes the species *M avium, M intracellulare* and *M chimaera*. MAC is classed as a slow-grower.
• *M abscessus* complex (MABSC) are rapid growers and this group are now the commonest found in the UK, and include the subspecies *M abscessus abscessus, M abscessus massiliense and M abscessus bollettii.*

Other species can be found, they include *M kansasii, M xenopi, M malmoense, M fortuitum* and *M simiae*. Their role as a pathogen is poorly understood.

The natural history of NTM disease may vary between species; a recent epidemiological study and several case reports suggest that *M abscessus* complex follows a more fulminant course and is associated with a poorer outcome.

The prevalence of NTM among CF patients, based on a large multicentre trial undertaken in the US, where NTM was defined as at least one positive NTM culture, is 13%. The UK CF Registry suggests 2% of all children with CF have at least one positive NTM culture in a given year (2021). 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 or macrolides, allergic bronchopulmonary aspergillosis (ABPA), *Pseudomonas, Staphylococcus* or *Aspergillus* chronic infection, and deteriorating lung function, but these have not been found consistently.

Accurate recording of the organism isolated in a child must be used in all their letters, clinic summaries etc., it is not good enough to use the umbrella term NTM as the consequences are so different.

Monitoring for NTM infection

Acid fast bacilli (AFB) smear and cultures for NTM are performed on sputum, induced sputum (IS) and BAL samples, our centre does not perform NTM cultures from cough swabs. Samples are sent:

- At annual assessment visit (if productive of sputum)
- In a child who is unwell but culture-negative i.e., clinical concern
- On any child having a bronchoalveolar lavage
- On any child having an induced sputum
- On admission for a chest exacerbation
- Already known to have cultured NTM

If NTM is isolated from sputum – 2 further samples should be requested, preferably over a 2-month period to allow for natural clearance of the NTM. In our recent audit 10% of MABSC and 40% of MAC cleared spontaneously. A single isolate of NTM should NOT be treated, unless from a BAL (or induced sputum). The decision to treat is a consultant consensus one. It is important to ensure symptoms are not wrongly attributed to NTM, and other causes have been treated before NTM treatment is started. Some NTM can be present as commensals and have no significant effect on respiratory function or nutritional status. The exception is *M abscessus* complex, which generally causes significant lung disease. Azithromycin monotherapy should be stopped whilst awaiting confirmation of a diagnosis of NTM pulmonary disease.

Our laboratory will identify the sample at "complex" level on the first positive sputum sample e.g., *M abscessus* complex will appear on the report. When a second sample is positive this will be identified at species level e.g., *M massiliense* and antibiotic sensitivity testing will be performed, subsequently the lab will report the *M massiliense* as *M abscessus* complex again. Speciation and sensitivity testing is performed on first sample for BAL samples. Isolates are sent to the reference laboratory for molecular typing. Species level identification and sensitivities are done yearly on patients remaining positive.

Infection control (see section 4.7)

M abscessus complex:

- In-patients - kept in complete isolation on the ward.
- Clinic - seen only in 2nd wave (3.15) slots in clinic so that the room is not used again that day.

Other NTMs:
- In-patients – standard segregation for patients with CF.
- Clinic - only in 2nd wave (3.15) slots in clinic so that the room is not used again that day.

Treatment of NTMs - principles

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 known as NTM pulmonary disease (NTM-PD). Some NTM can be present as commensals and have no significant effect on respiratory function or nutritional status. Not all patients will benefit from treatment for NTM. In 2016 the European CF Society and the US CF Foundation published consensus recommendations on the management of NTM in CF [see Floto et al, Thorax 2016;71 Suppl 1:i1-22. Available on http://thorax.bmj.com/content/71/Suppl_1/i1.full.pdf+html].

Patients are defined as having NTM-PD if they meet clinical and radiological criteria with positive cultures from two or more separate expectorated sputum samples, or from a single BAL 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. The presence of HRCT changes attributable only to NTM is very hard to confirm in the presence of similar radiological findings occurring in CF and ABPA. 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; starting treatment is by a consultant consensus decision and based on the risks and benefits of treatment for each individual.

Treatment should be tailored according to the specific species of NTM, which will be considered separately. Generally, *M avium* complex is treated with three oral antibiotics, largely irrespective of sensitivities, for 18 months. Whilst for *M abscessus* complex, typically there is a 3 week intravenous induction phase, which may need to be repeated if the child deteriorates during the consolidation phase. Consolidation is for 18-24 months with four medications, usually a combination of oral and nebulised.

Stopping Treatment for NTM

Patients are treated for at least 12 months after the first negative NTM culture whilst on treatment (culture conversion). Treatment can then be stopped *(consultant decision).*

Patients are considered free of NTM when they have had 4 negative samples over a year after stopping treatment. This means they cannot be considered truly negative until at least 1 year off treatment. **This is effectively 18 months to two years after first negative sample.**
If NTM was only isolated on a BAL or induced sputum in a non-sputum producing child, a repeat BAL or IS will be needed to stop treatment and again at a year off treatment. IS should also be used in between these time points. Only then will they be considered negative.

Patients who fail to clear MABSC may be considered for long term suppressive therapy, this may take the form of nebulised therapy or long term dual oral therapy (consultant decision).

Treatment of *M abscessus* complex

M abscessus complex is usually multi-resistant. However, if possible, initial antibiotics can be chosen according to sensitivities.

Dosage and Administration

The regimen in Table 1, based on a 3 week initial 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 continuation therapy will be regarded as 'failing' treatment or relapsing if they have the following:

- Persistent positivity on sputum AFB smear at 6 months or earlier
- No response to treatment with non-mycobacterial antibiotics
- Increasing sputum and breathlessness
- Fevers
- Sweats
- Rising CRP

In this case they will be given second line intensive and continuation treatment, as charted in Table 3. Treatment is individualised so table 3 is just an example of a possible combination.

Continuation treatment should include four drugs in total (either nebulised or oral preparations).

If a patient is admitted with an exacerbation during their continuation phase, then all the continuation drugs should be continued whilst being treated with the intensive phase drugs (except minocycline/doxycycline which should be stopped if tigecycline is used; and nebulised amikacin stopped if IV amikacin is used).

On admission for Intensive (initial) phase:

- An **ECG** will be conducted to measure QT interval on those starting NTM therapy due to long term use of azithromycin, moxifloxacin, ondansetron and possibly clofazamine. The computer readout cannot be relied upon so the ECG must be shown to Dr Jan Till or Dr Leonie Wong, consultant cardiologists at RBH before starting the therapies.

- All patients should be adequately hydrated with IV fluids overnight prior to starting intensive IV treatment, a dose of IV ondansetron should be given prior to the first dose of tigecycline and/or cefoxitin; this may later be swapped to oral ondansetron. Both cefoxitin and tigecycline can cause significant nausea.

Table 1. First line intensive & continuation therapy for *M abscessus* complex. Doses in formulary.

Intensive phase therapy (duration 3 weeks)

Amikacin *IV*
Meropenem *IV*
Cefoxitin *IV* (2 weeks only) or Tigecycline *IV* (12 yrs+ see below re dentition)
Azithromycin *Oral*
Continuation therapy **(duration ≥ 18/12 depending on response)**
Amikacin *nebulised*
Moxifloxacin *oral*
Minocycline *oral* (12 yrs+ see below re dentition) or Co-trimoxazole *oral*
Azithromycin *oral*

- Cefoxitin is now only used for 2 weeks at a time due to the high occurrence of drug reaction e.g., rashes, fevers, DRESS syndrome (section 6.2b) with longer use.
- Decision of cefoxitin vs tigecycline is based on antibiotic sensitivities and age of the child.
- Some patients find that the continuation treatment also causes nausea and may need to continue oral ondansetron long term. Adjustment of drug dosing schedules may help this. Second line anti-emetics are sometimes used e.g., aprepitant (see formulary).
- Avoid minocycline, doxycycline and tigecycline in patients less than 12 years of age, unless a dental assessment has been done and tetracycline drugs are considered safe because secondary dentition is complete.

Table 2. Alternative drugs if patient is unable to tolerate or has side effects to any of the first line drugs for *M abscessus* complex. Doses in formulary.

Unable to tolerate	Consider
Moxifloxacin	Ciprofloxacin *oral*
Minocycline	Doxycycline *oral* (12 yrs+ see below re dentition) or Co-trimoxazole *oral*
Azithromycin	Clarithromycin *oral*
If macrolide-resistant, to replace azithromycin	Clofazamine *oral*

- Avoid minocycline, doxycycline and tigecycline in patients less than 12 years of age, unless a dental assessment has been done and tetracycline drugs are considered safe because secondary dentition is complete.
- Further alternative is linezolid which we would tend to only use for 6 months, with careful monitoring of eyes and white cell count.
- If macrolide-resistant, use clofazamine instead of azithromycin. ERM+ve are susceptible to be macrolide-resistant, but we only stop AZM if confirmed resistant, we do not switch based on ERM status alone

Table 3. Second line intensive and continuation therapy for *M. abscessus* complex. Doses in formulary. *(Changes only made after consultant consensus decision).*

Intensive phase therapy (duration 3 weeks)
Amikacin *IV*
Meropenem *IV* *or* Ceftazidime/avibactam *IV*

Tigecycline *IV* (12 years or over) (see below re dentition)
Azithromycin *oral* or Clofazamine *oral*
Continuation therapy **(duration ≥ 18/12 depending on response)**
Amikacin *nebulised* and/or Meropenem *nebulised*
Minocycline *oral* (12 years and over)
Azithromycin *oral* or Clofazamine *oral*

- 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, unless a dental assessment has been done and tetracycline drugs are considered safe because secondary dentition is complete
- Tigecycline can cause nausea. All patients should be adequately hydrated with iv fluids overnight prior to starting intensive IV treatment, a dose of IV ondansetron should be given prior to the first dose of tigecycline; this may later be swapped to oral ondansetron.
- If unable to tolerate tigecycline due to vomiting the dose can be reduced to daily or alternate day dosing or 2 days out of 3.

Failure to convert to AFB negative or culture negative at 6 months and later

- Children will have an induced sputum 3 monthly for the 1st year, and if IS not successful will have a BAL at 6 months.
- If sputum/BAL has not converted to culture negative by the 6 month stage, consider a 2nd trial of eradication with an admission for further intensive course of IV antibiotics. Consider using other oral antibiotic combination.

- Persistent failure to eradicate in a child who is severely affected by the M abscessus – we may consider Interferon gamma subcutaneous injections although not in the national guidelines, and it will require confirmation of funding from the patient's CCG via an Individual Funding Request (IFR) form prior to commencing treatment.
- Bacteriophage treatment has not been used by our service; some case reports show promising results.
- Other third or fourth line drugs considered for use are Tedizolid and Bedaquiline. All of these are consultant decision and would need IFR forms prior to commencing treatment.

Counselling - general

- Patients will be counselled on the treatment regimen for MABSC, 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.
- Hearing impairment may result from accumulative effects of nebulised amikacin, patients are advised to report any hearing problems or development of tinnitus. N-acetylcysteine will be used to protect ears with IV amikacin.
- Amikacin must be stopped immediately if there are any balance problems. • Patients will be advised to report side effects of treatment as soon as possible.

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 3-4 monthly intervals unless stated otherwise in drug monographs.
- A baseline hearing test should be performed in children at the start of intensive therapy with IV amikacin.

Treatment of *Mycobacterium avium* complex (MAC)

It is recommended that the following treatment regimen is used for a minimum of 12 months after NTM culture conversion.

Dosage and Administration

Initial therapy should be triple oral therapy as listed in Table 4. Patients who are unwell should begin by having 2 weeks intravenous therapy with amikacin and meropenem. As with MABSC treatment we would consider the NTM to be eradicated when sputum samples are free of NTM for a 1 year period after stopping treatment.

Table 4. Drug treatment for MAC. Doses in formulary.

Oral drugs
Moxifloxacin

or Ciprofloxacin if weight<40Kg
Azithromycin
Ethambutol

We have switched rifampicin to moxifloxacin or ciprofloxacin, due to interactions with Kaftrio.

If sputum does not convert to negative within the first 4-6 months of treatment, consider adding nebulised amikacin or using an IV "intensive" admission.

Counselling - general

- Patients will be counselled on the treatment regimen for MAC, 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.
- Patients will be advised to report any potential side effects of treatment such as jaundice, itching, and visual disturbance as soon as possible.

Monitoring - general

- Full blood count and the patient's renal and hepatic function must be checked prior to initiating treatment.
- Visual acuity should be measured before starting Ethambutol
- Renal and liver function should be checked at 2 weeks. If LFTs are raised to five times the upper limit of normal at any stage, all drugs should be stopped, and drugs restarted one at a time when bloods are back to normal with regular LFT and renal blood monitoring on re-introduction. If raised below 5x upper limit consideration should be given to stopping the rifampicin and ethambutol in the first instance, again with re-introduction slowly.

Treatment of other NTM

Treatment of other NTM should be guided by the sensitivities of the organism and should include a combination of at least 3 drugs. Treatment is given for a minimum of 12-18 months as for MAC.

6.2a 6 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. High dose IV co-trimoxazole (*P jiroveci* treatment dose) may also be considered (consultant decision), and it may be necessary to start at a lower dose and work up.
- 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 yrs or above, or >8 yrs if adult dentition confirmed by a dentist), depending on the sensitivities.
- For established chronic infection nebulised colistin is used long term, with nebulised meropenem as 2nd line.

6.2a 6 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.

6.2a 6 X *Rothia mucilaginosa*

Rothia is common in the oral cavity and is found occasionally in CF patients who have *Pseudomonas aeruginosa* and may promote growth of *Pseudomonas* via its metabolites. It may be a lower respiratory pathogen in immunocompetent and immunocompromised patients, but its pathogenic role in CF is uncertain. It is unclear if or when if to treat this, but if we repeatedly grow this organism, we will consider oral treatment (check sensitivities).

6.2a 6 XI. Specific gram negative organisms – *Klebsiella* spp, *E.coli* and other coliforms

We always treat the first isolation, and subsequent isolations if the child is unwell. Treatment is typically with 2 weeks oral co-amoxiclav. When repeatedly grown we treat gastro-oesophageal reflux aggressively with omeprazole and may consider a pH study. However, we prefer not to continue omeprazole long term as it is associated (in a non-CF context) with greater risk of respiratory infections.

6.2a 6 XII. Influenza

NICE guidelines 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. However, treat on clinical basis, do not wait for viral confirmation.

6.2a 6 XIII. RSV (Respiratory Syncytial Virus)

Infants with CF can get RSV in the same way as any infant. We do not recommend prophylaxis with palivizumab (see section 10.2). There is no specific treatment offered for RSV. However, we recommend oral antibiotic prophylaxis or if the baby is unwell in hospital, we would suggest IV antibiotics (ceftazidime & tobramycin). Infants with CF who have had RSV are likely to have infection with Pseudomonas aeruginosa sooner so microbiological vigilance is required.

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 (< 6months 250microgram/kg (max 2.5mg); <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 months 25mg; <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 drug chart.
- Inform consultant.
- Make sure child and family know which the offending antibiotic is, and this information is written all over the notes and becomes part of that child's diagnostic list on letters and summaries.

Most 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 recognise 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. If there is diagnostic doubt, consider referral to the Brompton monthly Wednesday allergy clinic run by the St Mary's Allergy service.

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 paediatric 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.

DRESS syndrome

DRESS SYNDROME is a rare, life-threatening drug reaction. The main cause of death is acute liver failure due to hepatic necrosis. DRESS is most often seen in CF in the context of *M Abscessus* induction chemotherapy, but many antibiotics have been implicated. DRESS typically develops 2–6 weeks after the first exposure to the causative drug but may come on sooner. Medications started less than two weeks before, or more than two months after, the onset of symptoms can generally be ruled out as potential triggers.

DRESS characteristically presents with rash, fever, haematological abnormalities and internal organ involvement. There is typically a prodrome of fever and pruritis for up to two weeks before the development of an upper body macular rash. The rash later becomes widespread and polymorphous, with variable development of pustules, purpura, vesicles and indurated plaques which may be followed by erythroderma, and diffuse scaling may follow. Other typical features accompanying the rash include facial oedema, tender lymphadenopathy, and mucous membrane involvement. Leucocytosis and eosinophilia are common.

The initial presentation can be difficult to differentiate from other delayed hypersensitivity reactions, and a high index of suspicion is needed. The liver is the most commonly affected internal organ ($\geq$ 75% of cases), severity ranging from asymptomatic mild transaminitis to acute liver failure, followed by the kidneys (interstitial nephritis) and lungs (interstitial pneumonitis). DRESS is a clinical diagnosis, which may be facilitated by a scoring system.

Assessment of causality is generally made clinically; patch testing is of uncertain value. In most cases, recovery is complete over the several weeks after the causative drug is stopped. However, affected individuals appear to have an increased risk of future drug hypersensitivity reactions and of later developing autoimmune disease.

Adrenaline auto-injectors

It has been advised by the CF Trust that all patients who receive the full course of IV antibiotics at home should have an intramuscular adrenaline auto-injector (*e.g.*, Epipen, Emerade, Jext). 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 adrenaline auto-injector 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 adrenaline auto-injector. In the UK, the practice of prescribing an adrenaline auto-injector 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 6.2d). Additionally, any child, who has had a previous allergic reaction to an IV antibiotic, must have an adrenaline auto-injector at home if receiving further home IV antibiotics.

Desensitisation

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 reactions, denying patients 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. The outcome of the desensitisation procedure must be documented in the medical notes, and if a reaction occurred, the exact nature of the reaction must also be documented.

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 patient's admission.

We carry out the full procedure for those with significant reactions e.g., DRESS syndrome, anaphylaxis, and this is done every time they are to receive the drug.

Full desensitisation

- 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 process, which takes about 2–3 hours, the patient is observed for signs of allergy.
- If all 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 team 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 part of the drug chart.
4. Each of the drug solutions will be administered to the patient as 20 minute infusions. Once an infusion has finished, the next one should be started immediately. The entire process will take approximately 2-3 hours.
5. Adrenaline, Chlorphenamine and Hydrocortisone should ALWAYS be prescribed on the 'when required' (prn) part 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 nauseous which can usually be relieved with the use of a regular anti-emetic.
7. If a reaction occurs, the reaction and its exact nature must be documented in the patient's medical notes.
8. If the patient tolerates the desensitisation regimen, the final dose should be prescribed on 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 full desensitisation process will need to be repeated.

Mini (partial) desensitisation

Alternatively, for patients thought to be at low risk of being allergic to a given drug, for example having had a mild rash previously, a graded drug challenge may be useful to 1) exclude hypersensitivity and 2) confirm tolerance. It is **not** suitable for patients who have had

severe reactions, and use of a challenge such as this should only be carried out after discussion with the consultant.

An example of a graded drug challenge regimen for final dose Ceftazidime 2g (2000 mg)

- Ceftazidime 2mg IV at 0600 (i.e. 1/1000th of the intended dose)
- Ceftazidime 20mg IV at 1400 (i.e., 1/100th of the intended dose)
- Ceftazidime 200mg IV at 2200 (i.e., 1/10th of the intended dose)
- Ceftazidime 2000mg IV at 0600 (i.e., intended dose)

As for the full desensitisation procedure above:

- 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 drug challenge, the procedure should be stopped, and no further attempts should be made to administer that antibiotic to the patient.

If the child has had a successful symptom-free mini desensitisation on 2-3 occasions, they could receive the normal dose the next time.

6.2c 3-monthly IV antibiotics

Currently less than 3% of our patients have regular 3-monthly IV antibiotics, and this figure has been reducing over the last 5 years. This tends to be in those with a more rapid decline in CF lung disease, which may or may not reflect the amount of treatment received at home. When we find children are having 3-4 courses IV antibiotics anyway, it is easier for families to plan the admissions in advance. We will try to arrange a date for the next course at the time of discharge.

Generally we try to stick to these guides –

- Consider whether a portacath would be helpful.
- Courses must be at RBH at least every other time (with the alternate being at home or local hospital).
- We will try to use aminoglycosides only on alternate courses.
- We will use oral N-acetlycysteine every time aminogycosides are used.
- Parents are to sign consent form for use of aminoglycosides.
- Audiometry testing at start and then annually.
- After 1 year consider whether regular courses are still necessary and document this. Usually we move to 4 monthly courses before stopping regular IV antibiotics. If 3-monthly regimen is continued beyond a year, then reconsider at least annually and document at annual review.

6.2d Home intravenous antibiotics (IVABs) and the Rose@Home Programme

In 2021 during the COVID-19 pandemic, Rose@Home was developed to allow children and families to complete courses of IV antibiotics (IVABs) at home with the virtual support of the

whole MDT. The programme aims to replicate a hospital stay at home. It allows families the flexibility of completing IVABs at home which can facilitate school attendance, less family disruption and less risk of cross infection; whilst also receiving tailored daily plans for MDT input.

Using the criteria in the hospital's Home IV antibiotic policy patients are carefully selected for Rose@Home. For example, it is not appropriate if the child is medically unstable or there are safeguarding concerns.
Each family receives an individualised timetable with online sessions from the physiotherapist, dietician, nurse specialist, and pharmacist as well as virtual ward round with the medical team. The timetable will be created in partnership with the family to encourage as many of the usual daily activities as possible, such as attending school.

Full details of the Rose at home programme can be found on the Standard Operating Procedure on RBH Teams (go into Teams, then click on Teams icon, then Rose@Home is listed), and is available to shared care teams on request.

Rose at home will be the preferred option for families wishing to undertake home IVABs, however there will be cases when this is not possible and, in those circumstances, the standard home IVAB protocol will be used. Whether using Rose@Home or regular home IVABs the following points are to be followed:

- 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 or the nurse in charge of the ward 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 they are happy to do so again. 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 MDT as to whether Home IV therapy is the most appropriate method for that specific occasion.

- Patients requiring >1 course IV antibiotics per year should have at least one (or part of) course of treatment in hospital per year.

- Antibiotics must be ordered (on the Baxter At Home prescription form) 48 hours before IVABs are due to start therefore prescriptions need to be handed to the paediatric pharmacy team by 12 pm at the latest. Prescription pads can be found on Rose Ward, outpatients and in pharmacy.

- Shared care doctors can email over requests to the CNS team (email addresses can be found in the contact section or contact the Respiratory Registrar on call directly via the hospital switchboard.

- Families should be warned about the risk of acute renal failure with intercurrent diarrhoea and vomiting or use of nephrotoxic drugs like NSAIDs if an aminoglycoside is prescribed. In that event, doses of aminoglycoside should be withheld pending our assessment.

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 an elastomeric infusion device.

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

- Families should be directed to the online resources and how to videos available here: Home Intravenous (IV) therapy service | Royal Brompton & Harefield hospitals (rbht.nhs.uk)

Patients must have their 1st dose of antibiotics on Rose ward/Day case 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 if not undertaking Rose@Home.
- Aminoglycoside levels or Us & Es (if on Colistin) must be arranged and booked.
- If completing Rose@Home, all review dates will be arranged within the timetable. However, if not 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.
- If not on Rose@Home programme CF paediatric physiotherapy homecare team alerted, and verbal contact or home visit arranged.
- OPA or day case review at the end of the course prior to line removal.
- Arrangements for line removal.

6.2e 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 significant procedural anxiety (needle phobia) because needle insertion is still required monthly for flushing. However, for many children with CF who have tolerated several, time-consuming and challenging venous access and as such are becoming more fearful of each new occasion, a portacath can be helpful. As

such, each individual child's situation will be considered involving input from the child's family and MDT.

- Consider replacing ports (if still required) after 3-5 years to prevent complications arising.
- Removal of a port should be considered if it is no longer clinically indicated.

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 must 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 at least 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/radiologist - Mr Simon Jordan or Prof Simon Padley 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. 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 15mg/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/diclofenac when patients are taking aminoglycosides or have significant liver disease. 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. Post op hydration also important to avoid severe constipation.
- 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** – Manufacturer recommends 4-6 weekly flushing with 3ml 0.9% sodium chloride followed by 4mls of heparinised saline (ready-made as 200 units per 2 mls). In practice, this is usually stretched to 8 weeks (and was 12 weekly

during pandemic with no adverse issues). 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 and also the correct length!).
- Always use aseptic non-touch 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** – difficulty may be due to lack of experience. If this is an issue, discuss with nurse in charge or CF 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. If urokinase not available use alteplase (Cathflo): dose >30kg: 2mg alteplase in 2ml of reconstituted solution; <30kg: dependent on volume of catheter size, 1mg in 1ml (max 2mg). Dose may be repeated after 120 mins if needed (max 2 doses).
- **Port leak** – a hole or break in the catheter may occur. 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 COVID-19

See also section 4.7 – infection control

COVID-19 is caused by the coronavirus SARS-CoV-2. Several coronaviruses causing common cold type symptoms have been circulating in the general population, especially in children for many years. SARS-CoV-2 first appeared in 2019, it spread rapidly causing a global pandemic that is still on going as these guidelines are being updated. Several variants

(strains) of the original virus have been reported over the last two years causing peaks or waves of infection, these travel the globe. It is common for viruses to mutate into different strains, they will often exhibit variations in disease severity and increased rates of transmission.

By March 2022 over 2000 people with cystic fibrosis in the UK had reported having had COVID-19. Studies of COVID-19 disease in people with CF show that risk factors for severe infection requiring hospitalisation include being post-transplant, having low lung function, being of older age, having CF-related diabetes and being of a minority ethnic group. Children in general have a milder disease. The introduction of the triple combination modulator Kaftrio has been shown to be associated with milder disease.

Treatment for COVID-19 has rapidly evolved with steroids being an established treatment for severe disease in hospitalised children. Other monoclonal antibody treatments are also available, research into other treatments is ongoing and inpatient treatment follows current national guidance.

As for other respiratory viral disease, we cover with oral antibiotics, if the child develops a productive cough during the COVID-19 infection, we use azithromycin or co-amoxiclav, dependent upon the child's previous microbiology results. Most children recover in 24-48 hours, often only having a fever and antibiotics are not required in these cases.

Vaccines were developed during 2020 and have been rolled out across the globe. They protect against severe disease and appear to reduce the symptoms. People with CF were prioritised for these vaccinations. In the UK they are currently recommended for children aged 5 and over, this age is lower in some other countries. Booster vaccine programmes are likely to be offered for some years.

We recommend children with cystic fibrosis follow the recommended vaccine schedule in the UK, this currently includes having the COVID-19 vaccination.

6.4 Fungal disease

6.4a *Aspergillus fumigatus – infection & ABPA*

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 can produce many toxic and allergenic exoproducts. It can cause several lung problems in CF. In general, we advise avoidance of situations where there can be high levels of this fungus: mucking out stables (it is commonly found in damp hay), building sites (common when knocking down old buildings), and exposure to compost (heaps and bags). In general, if children insist on horse riding this must be done out in the open, and they should avoid being inside the actual stable.

There are rare reports of an ABPA-like picture being a complication of other fungi (allergic bronchopulmonary mycosis).

1. **Allergic bronchopulmonary aspergillosis** (ABPA) is a serious potential cause of lung damage in CF (prevalence varies 0.6 - 11%). Early pick-up depends on screening and high clinical suspicion. We perform baseline screening at annual review with blood tests

(total IgE, Specific IgE, IgG ICAP). All sputum/BAL samples are tested for it. Galactomannan levels in sputum and BAL are also being measured although the diagnostic value of a raised level for this test is not yet fully understood in children with CF. They have been evaluated in adults with chronic pulmonary aspergillosis where they are found to be useful.

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 these criteria – maintain a high index of suspicion and discuss with the Consultant if in doubt.

Clinical –

- Increased wheezing/chestiness/chest tightness/chest pain particularly if failing to respond to antibiotics and inhaled medications.
- Fever and malaise.
- Thick sputum with brown or black bronchial casts (can appear spongy).

Investigations –

Major Criteria

- CXR pulmonary infiltrates > 1cm diameter and segmental collapse.
- High serum IgE - especially an abrupt recent 4-fold rise to >500 iu/ml, which falls with prednisolone therapy.
- High specific aspergillus IgE RAST. The normal value <0.35 kuA/L may rise 10-100x in ABPA. Note that level >5.7 is highly indicative of ABPA (100% sensitivity, 94% specificity).
- Positive aspergillus IgG (ICAP) >90 mgA/L 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 up to 30% of all CF patients).
- Brown/black plugs in sputum.
- Late skin test reaction.

NOTE Total IgE measured in IU/ml which = kU/L or kIU/L; 1 IU = 2.4ng
Specific IgE measured as kUA/L [A=allergen], often abbreviated to kU/L

Treatment -
For the first episode we use corticosteroids in conjunction with an oral antifungal agent - posaconazole. Because of CFTR modulator interactions, we are trying to reduce length of treatment courses.

Oral corticosteroids: **Prednisolone** is given at a starting dose of 2mg/kg/day (max 40mg) in the morning after food (not enteric coated as it is not well absorbed in CF). Since ABPA is invariably in older children, 40 mg is almost always the starting dose.

Regimen:

- Starting dose for 2 weeks – usually 40mg.
- Then reduce by 10 mg per week e.g., 30 mg for 1 week, 20 mg for 1 week.
- Ideally see in clinic at 4 weeks, and if markers and clinical state (including lung function) allows, reduce to 10 mg for 1 week.
- If 4 week clinic delayed, can reduce to 10 mg daily and stay on 10mg until seen.
- Then reduce to 5 mg daily for 1 week and stop.

If no improvement at 4 weeks, consider treatment adherence or whether there is continued exposure to environmental Aspergillus. Repeat total IgE at the end of treatment. Note though that in some cases who do well, the IgE fall may lag, so treat the patient not just the IgE level. Give them a Steroid Card. Screen blood and urine for glucose, and measure BP.

Varicella antibody (IgG) results should be checked when starting someone on oral steroids for ABPA. If negative the parents should be warned to be vigilant for possible chicken pox illness whilst taking steroids See section 10.2.

Pulsed IV methylprednisolone. This is attractive for the non-adherent patient, and may have fewer side-effects, at the cost of more inconvenience. We use IV methylprednisolone 10mg/kg ONCE (maximum 1gm) per day for 3 days every month. The 3-day pulses are usually given on 3 occasions, a month apart. Decision to use should be discussed with the consultant, and generally we would only use this first line in a patient known to be highly non-adherent.

Antifungal agents –

Posaconazole –
Is the drug of choice for all aspergillus lung disease and can be used down to 6 months of age. For ABPA this is used in combination with oral or intravenous corticosteroids

Azole anti-fungal medications are inhibitors of CYP P450 hepatic isoenzymes and cause increased levels of some drugs. Importantly a reduction of Kaftrio, Symkevi or ivacaftor doses will be required if an azole medication is started. Always check in BNFc and with a pharmacist to check for interactions

We always try to use tablets and they are **not** interchangeable with liquid on a mg for mg basis. **Treatment will stop when corticosteroids stop**. We are trying to reduce length of courses due to having to reduce CFTR modulator doses.

Posaconazole levels

- Pre-dose sample should be taken after patient has been taking for at least 1 week.
- Range: 1 – 5 mg/L.
- 1ml of serum into clotted blood vacutainers.
- Levels should be checked at 3 months if still taking it.

Itraconazole -
We no longer use this drug. The tablets are poorly absorbed, the liquid tastes horrid. Therapeutic drug levels are rarely obtained.

Toxicity monitoring for azoles

Liver function tests should be performed if blood is being taken anyway for repeat ABPA markers and at the time of taking posaconazole levels, 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). Blood glucose levels should also be taken at these times when on posaconazole because of the risk of raised blood glucose.
Beware of drug interactions *e.g.,* with rifampicin, CFTR modulators; and if azoles are given with inhaled corticosteroids this can cause adrenal suppression. Always check BNFc or with paediatric pharmacy team for interactions when prescribing.

Failure to respond to initial therapy (steroids and azole)

If clinical response is still poor:

- Consider IV methylprednisolone if oral steroids were used first line or consider further pulse of methylprednisolone.
- Check to see if serum level of posaconazole is therapeutic. If not, consider increasing dose and adherence before changing to other agent, taking note of any sensitivities available.

Relapses

Relapse is common, be alert to this possibility even up to 2-3 years after 1st episode. A repeat course of steroids (as above) will be needed, consider using IV pulse methylprednisolone if relapse has occurred within a year of first episode of ABPA. High doses of steroids may be needed for a long time, but the aim is always to try to use as short a course as possible so close follow up is needed.

Side effects are discussed in section 6.5 on use of steroids. A repeat course of antifungals will also be required as per guidance above, it may be worth considering an alternative azole at this time.

Hard to treat or frequently relapsing ABPA – other approaches

- **Nebulised amphotericin** (non-liposomal) may be used in difficult cases twice daily after physiotherapy (check for bronchoconstriction and use bronchodilator pre-dose). If it is essential to use it, and the child does not tolerate the normal amphotericin, consider using nebulised liposomal amphotericin; note the high cost. Treatment efficacy should be assessed at 1 month; courses are usually no longer than 3 months duration.

- **IV caspofungin** may be an option in refractory cases. Its use is a *consultant decision*.

- **Omalizumab** - the anti-IgE monoclonal antibody may rarely be considered based on case reports; this is a *consultant decision* and funding approval will be needed prior to starting. Subcutaneous injection every 2 to 4 weeks depending on IgE level and body weight.

- **Isavuconazole** – is a newer triazole anti-fungal increasingly being used for ABPA treatment in CF adults.

Postscript - we do not use voriconazole
Whilst it has better absorption than itraconazole and is not affected by gastric pH, its use is limited by side effects, particularly severe photosensitivity (in some cases despite use of high

factor sunscreen). With the MHRA alert highlighting the risks of squamous cell carcinoma following phototoxic reactions, as well as the risk of liver toxicity, we have effectively stopped using it. It would be exceptional and obviously is a consultant decision - record in notes that parents have had risks fully explained.

Liver function tests are mandatory (weekly for the first month and then monthly thereafter) and must not be forgotten. It is also imperative that patients are advised on sun protection.

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

2. Other manifestations of aspergillus lung disease

- **Positive culture only** - Aspergillus fumigatus almost never grows from cough swabs. It may be found in routine sputum, induced sputum and BALs; the significance of this in an asymptomatic child with normal ABPA blood markers is unclear. However, we will always try to eradicate it, especially if galactomannan levels are raised. We use 2 weeks of oral posaconazole and should check if eradication successful, with sputum or induced sputum.

- **Aspergillus bronchitis -** it is becoming increasingly clear that *Aspergillus fumigatus* causes more than ABPA, and aspergillus bronchitis is recognised in children who have grown Aspergillus in sputum and often have chronic respiratory symptoms or more exacerbations. They will usually show evidence of an immunological response (positive Aspergillus IgG (ICAP) >90 mgA/L) but no rise in total or specific IgE (*i.e.*, no hypersensitivity). We treat this with a one month course of oral posaconazole. Second line (if not eradicated) is a 3 month course of posaconazole.

- **Invasive disease** is very rare but may occur in severely debilitated, immunosuppressed (including steroids), post-transplant, or neutropenic patients. It is heralded by worsening of symptoms and progression of x-ray shadows, sometimes with cavitation, haemoptysis and pleuritic pains. Metastatic fungal spread is also possible. CT scan is useful to confirm the diagnosis. Such cases warrant treatment with IV caspofungin. Send BAL for galactomannan, it is an exo-antigen released by aspergillus hyphae when invading host tissue, so may help decide if aspergillus is invasive.

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

- **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 antifungal therapy

This is a *consultant decision* only and is made after consultation with microbiology.

- Severe, chronic and persistent aspergillus lung disease (including ABPA), with multiple side effects from conventional steroid therapy.
- Invasive aspergillosis
- Patients on NTM treatment requiring ABPA treatment when drug interactions may be problematic (*e.g.*, with rifampicin).

First line is caspofungin (it is easier to administer and cheaper). 2nd line would be liposomal amphotericin.

6.4b *Scedosporium apiospermum & Lomentospora prolificans*

Scedosporium spp. is the second commonest fungus isolated in CF respiratory secretions; ***Scedosporium prolificans* was renamed to *Lomentospora prolificans* a few years ago** and is highly drug resistant. Similarly, to *Aspergillus* it can cause fungal balls in cavities and can be found in paranasal sinuses. Clinical implications are poorly understood; it is often not associated with symptoms. We are now much more likely to consider early attempts at eradication especially if symptomatic but only after treatment for other causes of cough or exacerbation have been treated and excluded.

Difficult cases can be discussed with the Fungal team at RBH.

If treatment is considered, check sensitivities –
Scedosporium apiospermum – we will use **posaconazole** for 4-8 weeks. If fail to eradicate consider voriconazole which has a lower MIC.
Lomentospora prolificans – we will use **posaconazole + terbinafine** for 6-8 weeks.

The microbiology lab will supply azole sensitivities and treatment may be guided by these when available, although we would still try to avoid voriconazole because of the side effect profile.

Rarely, *Scedosporium* has been known to cause an allergic bronchopulmonary mycosis (similar to ABPA), and an azole should be used for this with consideration of corticosteroids, this will be a consultant decision.

6.4c *Exophiala dermatitidis*

This black yeast is commonly isolated from respiratory secretions from people with CF, but very rarely in non-CF patients. We may be seeing this more often due to the 28 day fungal cultures we use, or perhaps this reflects anti-bacterial policies. It may be a harmless coloniser but has been associated with respiratory deterioration in some cases. We would treat this if the child is symptomatic in the absence of other causes *e.g.*, bacterial infection. Dual therapy is required, usually terbinafine and an azole antifungal for 4-8 weeks.

6.4d *Candida species.*

Candida is commonly grown in sputum and cough swabs and is usually from the mouth. The use of long term antibiotics is usually blamed. Do not forget to ask about perineal *Candida*, it

is common in infants with nappy rash and can be present in older children. Local treatment with nystatin will be given if the child is symptomatic *i.e.*, sore mouth, visible white plaques. Alternative is miconazole. See BNFc for doses.

However, it is not expected to be found in BAL fluid (unless nasal approach is used where it still may be a contaminant from the pharynx). We tend to treat with up to 2 weeks of oral fluconazole if found in BAL (see BNFc for dosage). Very occasionally, in the absence of other organisms, clinical improvement has been seen with IV antifungal therapy.

6.5 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.
- 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 6.4. For severe bronchospasm, dose is 2 mg/kg prednisolone (max 40mg) administered in the morning after food, which will be reduced as soon as possible, depending on the response. We sometimes use intravenous methylprednisolone 10 mg/kg/day (max dose 1gm) for 3 days, repeated monthly – for severe cases and when adherence 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 & polydipsia. 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).

Indications for inhaled steroids

- Symptomatic wheezing that requires regular bronchodilators, in a similar regimen to BTS guidelines for asthma. Especially in atopic children and those with predominance of eosinophils in sputum or BAL. Ideally acute bronchodilator reversibility should be documented.
- We do <u>not</u> use it long term as an anti-inflammatory agent in an asymptomatic child.

We use budesonide or fluticasone, and occasionally ciclesonide (with its small particle size), but not usually beclometasone. Devices used depend on the age of the child, but nebulised steroids are not used. In older children, at low or moderate doses (<400 mcg/day budesonide, <200 mcg/day fluticasone) dry-powder inhalers (DPI) may be 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 1-2cm loss), oral candidiasis (so mouth must be rinsed, or teeth brushed and 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** (LABA) but only as a combination inhaler (e.g., Seretide or Symbicort). The patient must never take the LABA alone (without an inhaled steroid), so we do not prescribe salmeterol or formoterol inhalers. More often than not, we use combination inhalers rather than inhaled steroids alone.

6.6 Dornase alfa (RhDNase)

Note that Dornase alfa is drug name and how it appears in BNFc. Pulmozyme is trade name. We tend to call it DNase – the original name.

Dornase alfa 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%). A positive response may also be stability in lung function, *i.e.*, no decline.

Indications:
It should be a *consultant decision* to start dornase alfa in children less than 6 years old.

- Our policy was to consider starting dornase alfa for all patients when they are 6 years old, whatever their lung function (as per European CF Society recommendations). Our view was that it would be unusual for a child aged 6 and above not be commenced on it given the potential benefits and mechanisms of action.
- However, with the licensing of Kaftrio for children aged ≥6yrs in January 2022, and the likely benefit this will have on treating CF at the cellular level, the need for dornase alfa to reduce sputum viscosity and aid sputum removal in all patients of this age is no longer as clear-cut. We will no longer offer it routinely to a child starting Kaftrio at 6 years, or if they are already taking ivacaftor, assuming they have minimal lung disease. We would still offer it if we were concerned about the child's lungs *e.g.*, recurrent growths of bacteria, poor lung function or LCI, abnormal ventilation scans etc. We will also routinely offer it to children unable to take a CFTR modulator.
- For those already on dornase alfa we are continuing its use, but will wait for results of CF-STORM (patients ≥12yrs trial on whether stopping dornase alfa and/or hypertonic saline in patients on Kaftrio has an adverse effect on clinical outcomes, expected to be reported in 2023/24). It is likely these results could be extrapolated to patients taking ivacaftor.
- We would strongly suggest dornase alfa is used in any child
    - whose FEV_1 is <85%.

    - who hardly expectorates at all but has symptoms.
- We would consider it in preschool children if there is concern over their respiratory status (especially those with persistent cough relating to mucus plugging or with abnormalities on a ventilation scan) and have a low threshold, especially for those over 2 years of age, however we do not advocate routine use in under 6s.

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 6.15. It would be expected a child like this would already be on dornase alfa 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 showed a reduction in exacerbation rate and a slowing in deterioration of lung function. There seems to be no clinical difference between daily and alternate days treatment, but we mostly use daily dosing. A further study showed a reduction in overall DNA with dornase alfa use as a proxy for reduced inflammation.

The Cochrane review 2016 showed **no** dornase alfa lung function superiority compared to hypertonic saline in 3 trials and superiority in one trial – this is relevant in a cost-restrained setting although dornase alfa toleration is superior.

Dose - 2.5mg by appropriate compressor and nebuliser i.e., standard or faster E-flow or I-Neb (if using the I-Neb 1ml dornase alfa is nebulised and the rest is discarded). This is an expensive drug (about £6000/year used daily). RBH is responsible for the prescription, a new prescription is given by our pharmacy, with future prescriptions via the home delivery service. We must encourage home delivery as it saves the NHS 20% of the cost, since if prescribed directly from hospital pharmacy VAT is payable.

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

There is no evidence that increasing the dose to 5 mg once daily, or 2.5 mg twice daily gives extra benefit. Occasionally our physiotherapists will suggest it for in-patients having an exacerbation, and we would consider it, but would first try using hypertonic saline once daily alongside with dornase alfa once daily.
Timing - Timing is decided on an individual basis. In most cases it is given at least 30 mins pre-physiotherapy. Cochrane review states "RhDNase can be administered before or after ACT to suit the individual, although in children with well-preserved lung function FEF_{25} was improved if RhDNase was given prior to ACT. If RhDNase is given before ACT it should be a longer time interval than immediately before ACT". We believe it is best given 30 mins pre-physiotherapy. In exceptional circumstances, it may be given pre-bed if the child is having difficulty fitting in all their therapies – this is a consultant or senior physiotherapist decision; parents must monitor for excessive overnight cough.

Side effects: an exceedingly safe drug. Side effects are rare and mild such as hoarse voice occasionally and rash sometimes seen. There is **no** need to stop its use in patients with haemoptysis or pneumothorax

6.7 Hypertonic saline

Hypertonic saline (HS) is sodium chloride in solution at a higher concentration than normal saline (which is 0.9% equivalent 150 mmol/L sodium). Many concentrations are available in different countries (3%, 6%, 7% etc.). We almost always use 7% (but not higher concentration) as it is superior to 3% if tolerated. Its mode of action is to osmotically draw water into the airways to hydrate the mucus and aid clearance.

Indications:

a) Long term mucus hydrator. Should be considered in the same way as dornase alfa (section 6.6) and as a cheaper alternative. However, studies show that some patients respond better to dornase alfa and others to hypertonic saline, so a trial of therapy is important. We commonly use HS once a day in the morning immediately pre-physiotherapy and dornase alfa 30 mins before the evening physiotherapy because of the time lag between nebulisation and physiotherapy, and the feasibility of fitting in treatments around school.

b) **Use in infants** - Results from PRESIS and SHIP studies suggest an improvement in LCI of around 0.6 (compared to placebo) in children aged under 1 year and 3-6 yr olds respectively. This small but significant improvement must be weighed against the extra burden of treatment for young patients at an age when nebulisation is difficult. Subgroup analysis suggests this may be more relevant for those with worse LCI and older age, but numbers were small.

   Currently we are targeting patients we feel are most likely to benefit, *e.g.*, those taking lots of oral antibiotics, those with more respiratory symptoms, those with recurrent microbial growths etc. Experience over the last 3 years is that infants tolerate the drug response assessment in hospital, but a proportion (9/16) of infants did not tolerate regular use at home, although some then tolerated the 3% solution better.

   We have now decided to offer 7% HS twice daily routinely at 1 year of age unless they are already on ivacaftor. It is likely we will stop it if they start Kaftrio. We will check at 4 weeks how tolerating it, and if not going well try 3% HS.

   We will only start it in infants under 1 year if we re clinically concerned about their lungs.

c) Short term use in an exacerbation to aid removal of sticky secretions.

Risk of bronchoconstriction. Always give salbutamol 2-4 puffs of 100 mcg dose inhaler via a spacer before **every** dose and spirometry **must** be performed before **and** after the first dose in hospital prior to home therapy. Occasional patients must stop because of pronounced bronchoconstriction - FEV_1 reduced >15% (with or without symptoms), or by 10-15% with symptoms) despite salbutamol. It may then be worth trying 3% at this stage. In children too young for spirometry, we monitor oxygen saturation with auscultation for the 1st dose.

Dose: 4mls 7% or 3% HS once or twice a day via nebuliser just before physiotherapy. We use 7% or 3% sodium chloride in 4ml plastic ampoules. Prescribable by GPs.

How to give: By nebuliser. In the eFlow (or Pari) given in one go but always 1ml left. By I-Neb always use LILAC chamber and you must nebulise twice *i.e.*, 2ml each time. The new AeroEclipse breath actuated nebuliser nebulises to dry but there is no comparative efficacy data currently. Hypertonic saline (not dornase alfa) may be combined with an airway clearance device when there are adherence issues, e.g., Pari PEP and Pari Sprint, Acapella and Respironics side stream with a t-piece, Aerobika with Pari sprint, or Pari eFlow rapid. Our physiotherapists must teach children how to do this. The iNeb cannot be combined with an ACT device.

Side Effects: Bronchoconstriction (see above), and it really does taste salty! May have to titrate up from 3% in younger children and those who don't initially tolerate 7%.
Warnings: **Not** recommended to make up nebulised antibiotics with HS

6.8 Mannitol (Bronchitol)

Inhaled dry powder Mannitol (Bronchitol) is an osmotic agent (like hypertonic saline) that may increase mucociliary clearance in CF by improving cough clearance and rehydrating the airway surface liquid layer. A 2017 paediatric study in children aged 6-17 years was positive, demonstrating a reduction in pulmonary exacerbations and a small improvement in FEV_1. A NICE 2012 review (updated 2015) on the role of inhaled mannitol recommended its use in adults with CF. According to NHSE Commissioning Medicines for Children in Specialised Services this means we can use it in post-pubertal children if they fulfil the criteria outlined in the NICE guideline.
https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf

Mannitol should be considered third line (after dornase alfa and HS) in those who do not respond to dornase alfa and fail to respond to, or tolerate, hypertonic saline (HS).

Indications: Long term use in children with troublesome symptoms *e.g.*, unproductive persistent cough or very sticky sputum, and declining FEV_1 (more than 2% annually) not responding to either dornase alfa, HS or both.

Dose: 400mg twice a day. Comes in 40 mg gelatine capsules so 10 capsules via **specific** inhaler device - quite an onerous therapy.

Bronchitol Initiation dose assessment. Must be assessed by physiotherapist using the company's protocol. Available - http://www.bronchitol.info/assets/Uploads/2018-05-15-Bronchitol-HCP-Leaflet-UK-V2.2.pdf.

Side Effects: **Bronchoconstriction.** Must have spirometry pre and post first test dose and ALWAYS pre-treat with salbutamol 2-4 puffs. Up to 25% have significant bronchoconstriction despite salbutamol precluding its routine use.

Response: Highly individual, some really respond well, others effectively zero so a therapeutic trial and outcome monitoring is important.

6.9 Long term azithromycin

There are several indications for azithromycin:

a) As a conventional antibiotic (see section 6.2a) for treatment of respiratory infections especially if Mycoplasma or Chlamydia are being considered. It may have some antibacterial properties for *Pseudomonas aeruginosa*.
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.
c) **Part** of treatment of non-tuberculous mycobacteria (section 6.2a 6 VII)

Criteria for long term use: 6-month therapeutic trial for patients deteriorating on conventional therapy (including mucolytics), irrespective of their infection status.

Following results of COMBAT-CF study, we might consider long term use in children <3 years of age with concerning lung disease e.g., multiple admissions for IV antibiotics, multiple bacterial growths etc. We would not start it routinely, however.

Dosage: 250 mg once daily (<40kg) or 500 mg once daily (≥40kg) **three times a week** (Mon Wed Fri). Note this dose differs from that for acute infection.

Judgement of response: Onset of action is slow (at least 2 months) and a minimum 4, preferably 6 month trial is required. *If there is no improvement it should be stopped after 6 months. Put date started on letters so this is not missed.*

Side Effects: Theoretically liver function (LFTs) abnormalities and reversible tinnitus although only one transient LFT abnormality was observed during our study. LFTs should be performed at any time blood is being taken for other reasons and at annual assessment.

Long QT. We will not routinely do an ECG when starting long term azithromycin unless there is a family history of long QT or the child had previously fainted/had loss of consciousness. We will do an ECG if they are taking a 2nd drug that can affect the QT interval. The ECG must be checked with a cardiologist as we cannot rely on the computer readout.

There are some anxieties in the literature about Azithromycin acting as a single agent NTM treatment promoting either growth or resistance, although examining our own data and the US and French studies suggests no increased risk of isolating NTM in those on AZM. Indeed, we and the French study found that long term AZM may reduce the NTM risk. We will send a sputum or induced sputum looking for NTM before starting this therapy.

When long term AZM is started, consider stopping prophylactic flucloxacillin, unless there is a good reason to continue, *i.e.,* patient is known to have macrolide-resistant organisms.

We believe the evidence is not strong enough to suggest that azithromycin cannot be used at same time as tobramycin (IV or nebulised) so will continue current practice.

6.10 CFTR modulators

(for doses see Drug Formulary)

Modulators comprise two groups of small molecule oral drugs:

- **Potentiators** which require the CFTR protein to be in its correct location at the cell surface, and then increase the time the channel spends open. These were originally designed and tested in Class 3 (gating) mutations which lead to channels which are largely closed; they are also used to increase the activity of CFTR which has been 'corrected' with other molecule(s). This is ivacaftor.
- **Correctors** improve trafficking of misfolded Phe508del CFTR (and some other variants) through the cell to the surface. Those which were tested on their own in clinical trials were inadequately effective unless combined with a potentiator. Three correctors are now licensed: lumacaftor, tezacaftor and elexacaftor which are used in either two or three molecule combinations with ivacaftor.

Monitoring requirements, drug interactions and side effects are listed at the end of this section.

The full lists of eligible genotypes as approved by NHSE are provided on Future NHS website – https://future.nhs.uk, you must register to use the website. Put CFTR in search box and look for CF Off Label Look Up Table.

There is also a list of licensed genotypes provided by Vertex on https://www.cfsource.co.uk, but note that we can use the drugs on more genotypes than in the list of Vertex licensed genotypes. That list is also on the Future.nhs.uk website, look for CF Vertex Licensed CFTR Look Up.

6.10a Potentiator: Ivacaftor (Kalydeco)

Only one potentiator drug is currently licensed. Ivacaftor is approved from the age of 4 months (with trials recently completed for 1-4 month olds) for those with one or more gating mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D); NHS England have widened the list for which funding is available based on FDA approval of a range of lab-sensitive mutations. Trials have confirmed more modest efficacy in adults (but not children) with the class 4 (conductance) mutation R117H, and currently, adults and post pubertal children (essentially 14 years and above) with R117H are eligible for treatment. However, this only applies to those with CF disease and evidence of abnormal CFTR function, clinical or physiological (usually 5T); we would not start CFSPID patients, usually 7T, unless there were clinical concerns (consultant discussion); this applies also to the same group of patients with F508del on their other allele when considering Kaftrio.

Since the majority of these patients will have F508del on their other allele, and trials demonstrated additional benefit of correctors in this group, most of the 6yrs+ children will now be prescribed Kaftrio instead of ivacaftor. However, for those with gating mutation without F508del, but in whom 2nd allele still makes them eligible for Kaftrio, the switch is not made automatically if they are doing well with low sweat chlorides as the side effect profile of Kaftrio is greater than for ivacaftor alone. Options should be discussed with the family.

6.10b Correctors / potentiator combinations

The commonest CF gene variant, Phe508del, results in CFTR protein which does not reach the cell surface; one or more correctors are used to assist trafficking of the protein to the cell surface and ivacaftor then further enhances CFTR function. Three combination treatments are currently available:

6.10b 1 Lumacaftor / ivacaftor (Orkambi)

Clinical trial improvements were more modest than those seen with ivacaftor (2-3% FEV1) but impacts on rate of pulmonary exacerbation were more robust. It is currently available for children 2 years and older who are **homozygous Phe508del**. In practice it is used for 2-5 year olds, as those aged 6 and above can receive Kaftrio (below), which is more effective. In older patients, chest tightness was a relatively common early side effect; this seems less of an issue in younger children with earlier stage disease.

6.10b 2 Tezacaftor/ ivacaftor (Symkevi)

The second dual combination demonstrated similar efficacy to Orkambi but improved tolerability fewer drug-drug interactions. It is licensed for people from 6 yrs of age who are homozygous Phe508del or have a range of residual function mutations. One of these is D1152H which is common in the CFSPID cohort, in whom modulators are not indicated.

6.10b 3 Elexacaftor/ tezacaftor/ ivacaftor (ETI, Kaftrio)

The phase 3 studies in people 12 yrs+ were published in Nov 2019 and 6-11 yr old trials have since supported a license extension. Results were very positive (greater than ivacaftor effect in gating mutations) and the drug has a good safety signal (see details below).

Eligible population (based on EMA license plus a group granted access by NHS England in line with FDA approval:

- Any patient with at least one Phe508del
- Patients without Phe508del, possessing at least one of a range of other mutations

All children reaching this age and on Orkambi will be switched to Kaftrio. Children receiving ivacaftor will likely gain further benefit from Kaftrio if they fall into the groups above. Families should be counselled to this effect and switched over unless a good reason exists not to.

6.10c Dosing

For all modulator drugs there are common monitoring and drug interaction considerations.

All modulators currently require twice daily dosing, and it is crucial that they are taken with, or very shortly after, a high-fat meal or snack (with the usual pancreatic enzymes if used), as otherwise absorption is poor. Tablets must not be chewed.

Side effects

Drugs and combinations are, in general, well-tolerated.

- **Rashes** were common in clinical trials. Children who develop a generalised rash thought to be attributable to Kaftrio treatment should be monitored closely. Mild rashes may resolve spontaneously with continued treatment. Kaftrio should be stopped if the child develops a *severe* generalised rash unless another aetiology is highly suspected. Clinical teams should consider additional evaluation including laboratory testing (*e.g.* FBC and LFTs), or dermatology review. Kaftrio can be re-introduced once the rash has resolved; in the event of recurrence which is severe, drug may need to be stopped, although a trial of an adjusted dose (non-evidence based, case by case, consultant guidance) may be tried.

- **Liver function** - rises in liver function tests were observed in all trials in some patients, which in some cases required dose interruptions, although they can often be recommenced. Consider whether concomitant drugs may be contributing, e.g., antibiotics. Dose reduction recommendations are available for patients with *significant* hepatic or renal impairment (Appendix 6).

  If the child develops alanine transaminase (ALT) or aspartate transaminase (AST) >3 × upper limit of normal (ULN), or a total bilirubin >2 ULN this should be followed up. Repeat LFTs should be obtained within 1-2 weeks, depending on whether an obvious additional trigger has been identified (*e.g.* child being on a course of another drug with this potential). The child can remain on their modulator during this time as long as abnormal tests do not meet the criteria below. If the LFT increase is persistent or severe, investigation of potential other causes for raised LFTs should be considered (*e.g.* with liver ultrasound or viral screens). The child should be followed closely for clinical progression with safety netting for families. The frequency of subsequent repeat liver function testing should be determined by the trend in the LFTs and the clinical picture.

  The modulator should be interrupted immediately if any of the following criteria are met:
  ALT or AST >8 × ULN.
  ALT or AST >5 × ULN for more than 2 weeks.
  ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice.

  All children who have discontinued treatment for LFT disturbance should have these monitored closely until levels normalise or return to baseline. Clinical teams may consider resuming the modulator once transaminases return to baseline or are ≤2 × ULN, whichever is higher. Upon resumption of drug, LFTs should be assessed weekly for 4 weeks. If further disturbance in LFTs meet the interruption threshold within 4 weeks of rechallenge with Kaftrio then dose reduction could be considered on a case-by case basis (consultant decision). Alternatively, in a child demonstrating these LFT abnormalities on Kaftrio who had previously tolerated a dual modulator combination (Symkevi or Orkambi), reintroduction of that may be considered.

- **Mental health issues** - A small number of case reports have reported mood disturbance, anxiety or depression in people taking modulators, which in some cases have responded to stopping or changing the drug and have therefore been considered likely related. However, there are many other potential contributors to such problems, including re-evaluating the future, loss of the past due to ill health. There is no evidence on which to base any guidance, but general principles include a multidisciplinary approach to assessing the child in the context of the broader family, with an emphasis on psychology involvement. In a very severe case, interruption of modulator, a lower dose, or an

alternative agent may be considered after discussion with the family. This section will be updated if new information becomes available.

6.10d Monitoring

For all modulator drugs there are common monitoring and drug interaction considerations.

- **Eyes** – The finding of cataracts in neonatal rats exposed to high doses of ivacaftor in utero has led to additional vigilance in clinical trials and prescribed use; whether there is any link in humans is unclear. However, cases of non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with ivacaftor. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations (annually in those under 18 years) are recommended in paediatric patients initiating modulator treatment. We should tell patients that the check is for presence of cataracts or lens opacities, and we need written confirmation from the optician (do not need to see an ophthalmologist unless aged 5 yrs or below). There is a template letter for the opticians in appendix 5.
- **Liver function** – We want AST, ALT and bilirubin. Baseline or use results if taken within 3 months. Repeat 3 monthly for 1 year then at annual review unless concerns exist. When switching to Kaftrio (or an alternative modulator), the 3 monthly for a year regimen is restarted. Home fingerprick service cannot measure AST.
- **Blood pressure** – ensure measured in clinic for those on Orkambi, which has been associated with small but statistically significant group increases, and occasional hypertension in individuals. However, since this is now just 2-5 year olds unlikely to be an issue.
- **Sweat test** – not mandatory but ideally, we would do baseline and repeat at least once. This can be done in Network centres who are used to doing sweat tests. **Any child receiving CFTR modulator drugs as part of a clinical trial should not have sweat testing performed in the clinic for risk of unblinding.** Please contact Jane Davies with any queries.
- **Faecal elastase** – consider at baseline, at 6-12 months and perhaps annually for several years in children starting drugs at a young age. Otherwise, symptom-guided.
- **Mental health/ mood questionnaires** might be helpful and are done as part of annual review.

We will add to letters on all pts on CFTR modulators a section below diagnostic list – 'CFTR modulator management' to include date of last sweat test, liver function and eye tests.

6.10e Drug interactions – see appendix 6

For all modulator drugs there are common monitoring and drug interaction considerations.

There are some significant interactions, most importantly:

- **Azole antifungals**: (itraconazole, voriconazole, posaconazole) lead to inhibition of the breakdown pathways of ivacaftor, Symkevi and Kaftrio and accumulation of the drug. If co-administration is necessary, the doses of ivacaftor (monotherapy only), Symkevi and Kaftrio 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. Modulator levels are not currently available but sweat Cl^- could provide a useful surrogate for bioavailability. Note although dose reductions are not necessary for Orkambi, Orkambi reduces levels of itraconazole, voriconazole and posaconazole so an alternative antifungal should ideally be used.

- **Fluconazole** affects these pathways less than other azole antifungals but nevertheless manufacturers recommend reducing the dose of ivacaftor, Symkevi and Kaftrio to once daily.
- **Clarithromycin**: also leads to accumulation of modulators so manufacturer suggests reducing ivacaftor, Symkevi and Kaftrio to twice weekly. There is no interaction with azithromycin, we recommend using AZM instead.
- **Rifampicin, Rifabutin**: will significantly reduce modulator levels; co-administration not recommended.
- **St John's Wort:** as for Rifampicin.
- **Grapefruit** (or juice) should be avoided in patients on ivacaftor, Symkevi and Kaftrio as they reduce serum levels of these modulators. 'Lilt' fizzy drink does contain pure grapefruit juice, but in such small quantities, it is fine.

6.10f Drug provision

The medication is delivered by the hospital's homecare provider.

6.11 Haemoptysis

Streaky haemoptysis is common with chronic infection but may indicate deterioration so sputum should be cultured and a course of antibiotics considered. Haemoptysis must be differentiated from haematemesis. The source is usually from hypertrophied tortuous bronchial arteries supplying areas of chronic airway inflammation. *S aureus* is the one bacterium that has been identified to be associated with an increased likelihood of massive haemoptysis. 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. 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 dornase alfa is necessary, but if the child is taking NSAIDs, stop them. Consider stopping hypertonic saline in 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 –
- Mild haemoptysis with an infective exacerbation will normally settle without specific intervention.

For more severe cases -
- Give blood and correct coagulation defects if necessary (IV vitamin K/ FFP / cryoprecipitate).
- Start intravenous antibiotics; *S aureus* cover must be included.
- Continue with gentle regular physiotherapy, but omit chest clapping for 24 hours. This is essential so contact our physiotherapists for advice.
- Stop any NSAIDs.

Physiotherapy management –
There are no studies relating specifically to haemoptysis and chest physiotherapy. Instead, general advice is given based on clinical experience. It is important to continue with chest clearance to remove blood and infected secretions. These physiotherapy guidelines for haemoptysis are based on those used by the Adult CF Unit at Royal Brompton Hospital.

Management is aimed at clearing secretions without increasing the bleeding. This may result in temporarily stopping manual techniques, adjuncts and positive pressure and then reintroducing them gradually. It is preferable to wait 24 hours post-bleed before starting positive pressure, adjuncts or manual techniques (then only one at a time). In some cases, these will need to be restarted sooner for effective sputum / old blood clearance. This should be discussed with a senior member of staff.

- Initially ensure the source of blood is not from the mouth, nose or stomach.
- Next work out how much blood the patient has cleared in the last 24 hours.

<u>Positioning</u>

- It is useful to note the activity and position at the time of active haemoptysis. The weakened artery may rupture due to increasing heart rate or increasing the flow of blood when the area of lung supplied by the artery is dependent (bronchial arteries lie posteriorly so supine may exacerbate bleeding).
- If the patient can establish the location of the bleed, it is advisable to avoid chest clearance with the affected lobe dependent (bleeding lung down).
- If the haemoptysis is severe the bleeding location should be dependent (bleeding lung down) while the bleed is active to avoid asphyxiation.
- When the bleeding has subsided, you can place the bleeding lung uppermost to facilitate drainage as needed. Chest clearance can be resumed a couple of hours after active bleeding as per the moderate protocol.

<u>NIV</u> (it is rare for a child to be having NIV these days).
- In the presence of moderate haemoptysis NIV should be discussed with a senior adult CF physiotherapist and the medical team. If the patient is known to have type II respiratory failure and is on nocturnal NIV it is likely it will need to be continued.

- In the presence of massive haemoptysis NIV should be discussed with the physician/crash team.

Physiotherapy management in the presence of haemoptysis	
MILD Streaking or <5mls in 24 hrs. Sputum and blood mixed together	• Reassurance • Normal airway clearance regimen
MODERATE 5mls to <250mls blood in 24 hours Fresh blood 1 white sputum pot = 250mls	• Airway clearance techniques should minimise increases in intrathoracic pressure. • Airways clearance with ACBT or AD initially. • Minimise unproductive coughing. • Positioning – see below. • Avoid moderate and high intensity exercise. • Continue nebulised dornase alfa. • Consider stopping HTS or mannitol if causes coughing – discuss with senior. • Graded approach to reintroduce ACT if no further bleeding – in discussion with senior.
SEVERE > 250mls blood in 24 hours	• Urgent medical review. • Position patient with bleeding lung down. • Discuss with senior physiotherapist. • Oxygen / humidification. • When bleeding has subsided resume treatment as for moderate.
Post Bronchial artery embolisation (BAE)	• Chest clearance can resume after the procedure in consultation with the physician and radiologist. • Analgesia pre ACT may be required. • Start gentle exercise and build up. • Transient dysphagia is common afterwards.

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 and is used by our adult unit; for dose see BNFc.
- **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. Oral dose is 15-25 mg/kg tds (max 1.5 g/dose). IV dose is 10mg/kg tds (maximum 1gm/dose). It may be prescribed acutely as well (oral or IV).
- **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.

6.12 Pneumothorax

This is now rare in children. 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% - at least in the pre-modulator era) 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 needle followed by 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.
- It is very rare now, but 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. See section 6.18.
- Ensure attention to good hydration and prevention of constipation in the immobilised patient prescribed opiates.

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). There is anecdotal evidence of the use of endobronchial valve placement in people with

CF. 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.

There is controversy over how long after resolution can spirometry safely be performed. We have compromised to no spirometry for 6 weeks.

Remember also BTS guidelines about flying after a pneumothorax – need to wait at least six weeks, although families may wish to consider alternative forms of transport for 1 year after the initial event. Scuba diving is forbidden.

6.13 Intractable wheezing / severe small airways disease

At least 50% of CF patients are atopic based on 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 (and we have found with time a markedly rarer) group of patients characterised by -

- Little if any sputum production (despite large amounts in the chest).
- Wheezing.
- Tight chest.
- A severe obstructive lung function pattern.
- Often markedly abnormal LCI.
- 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.

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 adherence to treatment recommendations, 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? Ask about new pets in the household; there was a huge increase in pet ownership during the peak of the COVID-19 pandemic when we were not seeing most children face-to-face as frequently.

If these all negative:

- Consider CT scan to assess structural damage / bronchiectasis (including expiratory views).
- Consider bronchoscopy and pH study.
- Consider CF-related diabetes and perform a CGMS test (continuous glucose monitoring system).
- Consider adding other aeroallergens including house dust mite, tree and grass pollen, Alternaria and any pets that are in the home to the specific IgE panel.

Treatments –

- Consider using short acting β_2 agonists, 4-10 puffs 3-4 times a day via a spacer if necessary.
- **Combination inhaler** (**Seretide** or **Symbicort**) with inhaled steroid and a long-acting β_2 agonist (salmeterol or formoterol) can be considered as the next step. Symbicort (budesonide/formoterol combination) can be used regularly with extra 'as required' doses administered through the day (SMART regimen). Maximum we recommend is 400/12 twice daily with 4 extra doses of 200/6 allowed per 24 hours. Can also consider **Relvar Ellipta** dry powder (fluticasone furoate with vilanterol) since it is used once daily. Relvar 92mcg /22 mcg dose for a child >12 years: 1 inhalation OD. Please note the potency of fluticasone furoate. This is equivalent to 500mcg of fluticasone propionate/day (which is in Flixotide) or 1000mcg of beclometasone/day.
- **Inhaled steroids** - we would tend not to use inhaled steroids alone but as combination inhaler (as above). There is some evidence that steroids (oral and inhaled) increase the risk of isolating NTM so as always, a consideration of risks and benefits is required. Consider small molecule ciclesonide which theoretically allows better deposition of inhaled steroids in the lung. Other similar products are available.
- Consider **Tiotropium inhaler** – an antimuscarinic agent. Both Spiriva Respimat (dry powder) and Handihaler (MDI) state no data for use in CF, with the Respimat MDI product information stating not to be used in CF due to potential increase in adverse events/exacerbations. However there have been two publications using the Respimat in patients with CF that demonstrated safety with one study also showing improvement in FEV_1 over a 12-week period.
- Consider slow release theophylline – see BNFc for doses.
- Also consider IV aminophylline for an in-patient with severe wheezing (use standard acute asthma doses), an extremely tight expiratory huff, or obstructed flow-volume loop despite conventional treatment. See drug formulary for 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. This is given as an infusion over 30 mins, there is a risk of heart failure if given as a bolus. Blood pressure, urine dipstick for glycosuria and blood sugars must be monitored whilst on pulsed high-dose steroids.

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:

- **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.
- Long QT. We will not routinely do an ECG when starting long term azithromycin unless there is a family history of long QT or the child had previously fainted/had loss of consciousness. We will do an ECG if they are taking a 2nd drug that can affect the QT interval. The ECG must be checked with a cardiologist as we cannot rely on the computer readout.

6.14 The child in difficulty – CF Focus.

Some children are not progressing as well as they ought to. These children will be presented at our CF Focus meeting, held every 1-2 months with all members of the MDT represented as well as the child's named consultant. The proform is in appendix 17.

Generally, concerns are categorised as one or more of the following:

Lung health
- Spirometry worse than -2 Z-scores or dropping quickly.
- Three or more courses of intravenous antibiotics annually.
- Significant complications *e.g.,* haemoptysis, pneumothorax, therapy resistant ABPA.

Consider – induced sputum, bronchoscopy, CT scan, BDR, sleep study, LCI, exercise testing.

Nutritional health
- BMI < 2 Z scores below the mean; drop in weight or BMI centiles by 10% over a year.
- Significant feeding difficulties in the younger child or eating disorders in an older child.

Consider – CGMS, pH study, stools assessment, bloods. See section 7.1.

Glucose metabolism
- CFRD that is poorly controlled.

Consider – CGMS, admission to C&W under diabetic team. See section 8.1

Psychosocial
- Any child whose self or parent-reported symptoms are significantly different to what a clinician would expect (either over- or under-estimated).
- Any child whose everyday life functioning (school attendance, exercise tolerance) appears at odds to the objective clinical signs of disease severity.
- Any child in whom there is refusal or extreme reluctance to give prescribed treatments by the carers, or when the child refuses treatments.
- Safeguarding concerns.

Consider referral to clinical psychology, CAMHS, safeguarding team.

In these circumstances, the CF Focus meeting will decide if further investigations are necessary, any referrals to be made, and a treatment plan.

We will also do a **formal review of adherence** –

- Prescription uptake from GP, hospital (RBH & local) pharmacy and homecare provider.
- Downloading data from nebulisers when possible. Currently this is only available from an I-neb nebuliser for inhaled medications e.g., Promixin. In the future other companies e.g., Pari with their eTrack device, will be making this technology more widely available. The physio team aim to download I-neb data at least annually or more frequently if required.
- Home visit to assess medications.
- Blood levels if relevant *e.g*., prednisolone, posaconazole.
- When an in-patient, assessment under the SAM scheme (section 4.5).

We will also consider whether **environmental issues** need to be assessed especially if there have been no home visits before.

- Passive or active smoking, and vaping (salivary/urinary cotinine)
- Allergen exposure *e.g.*, pets, dust (RAST and skin tests)
- Home conditions *e.g.*, damp & mould, cleanliness including nebuliser cleanliness (very important if ABPA the issue).

6.15 Bronchoscopy

Indications in CF:

- 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).
- After eradication of new *P aeruginosa*, patients will all have an induced or spontaneous sputum culture. If they remain symptomatic and sputum culture was negative, they will have a BAL. We will not rely on a cough swab to prove successful eradication.
- **A cough swab / sputum sample must be taken on the same day prior to the bronchoscopy.**
- We try to obtain an induced sputum (usually in children above 2-3 years) before deciding on a bronchoscopy (section 6.16f), and this practice has meant we do far fewer bronchoscopies, certainly in older children. Arrange with the physiotherapy dept.
- **Therapeutic suctioning**:
- Persistent focal area of collapse / consolidation on chest x-ray, may also include instillation of dornase alfa (2.5 mg in 10 mls 0.9% sodium chloride). It is rarely of value when chest x-ray changes are generalised.

- **Other indications**:
- Intractable wheezing to exclude bronchomalacia.
- 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 (may be a non-bronchoscopic BAL) we will consider this.

Bronchoscopies are performed on Thursday or Friday afternoons in Theatres or the Imaging Centre, booking for in-patients is done through bed managers. Bookings for out-patients who are to be admitted are through the Bed Manager (ext. 82118). 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 often require minimum 48 hours IVABs after if significant secretions are seen. In practice bronchoscopy may be 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. Make sure PICC team booked to come to theatre unless the child has a portacath.

No other preparation is required, but a procedure-specific consent form must be signed. Patients must have no food or bottled milk for 6 hours, breast milk for 4 hours, and clear fluids up to 2 hours before the procedure.

It may be useful for a physiotherapist to be present during the procedure. Sometimes dornase alfa 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. If the dornase alfa is to be put in a small area, then use it neat (still 2.5 mg) and use 20 mls air in the syringe to ensure distal instillation.

Lavage

- Bronchoalveolar lavage fluid is sent to microbiology for culture (including NTM, fungi), virology for immunofluorescence, and cytology for fat-laden macrophages.
- Send BAL also for galactomannan if aspergillus suspected as it is an exo-antigen released by aspergillus hyphae when invading host tissue, so may help decide if aspergillus is significant. GM index <0.5 essentially excludes the condition, and results >3.0 virtually assures disease present.
- Lavage protocol – following CF SPIT study we have changed this to **6 aliquots of 1ml/kg lavage, from all 6 lobes**. Maximum lavage instilled is 6 mls/kg body weight, up to a maximum of 150 mls.

Biopsy

- If NTM is suspected (especially if aged 5 years and above), be sure to do bronchial mucosal biopsies, because granulomata confirming the presence of disease rather than transient colonization may be detected. This assumes safe to do so (i.e., patient does not have low platelet count from liver disease).

6.16 Chest physiotherapy

6.16a Exercise

Exercise is an essential part of care for the child with Cystic Fibrosis. Several studies have demonstrated that better aerobic fitness (peak oxygen uptake [VO2peak]) is associated with greater 7-12 year survival in people with CF. A thorough assessment and evaluation of

exercise can act as an early warning for clinical deterioration and should be discussed at every clinic or home visit. Annual exercise testing is recommended for all patients by the UK Cystic Fibrosis Trust and European CF Society.

Whilst CardioPulmonary Exercise Testing from 10 yrs age is gold standard, it is logistically not possible to do this every year, and other tests are available which are validated in younger children (≥ 6 years) such as 10m modified shuttle walk test (MSWT) or iSTEP.

Exercise has been shown to reduce sputum viscosity, improve ventilation and peak expiratory flow and facilitate the movement of mucus as well as many other benefits. Exercise prior to airway clearance can have an additive effect on sputum expectoration but it should be combined with forced expiratory technique (huffing, coughing and breathing control) to clear sputum effectively.

Factors to consider in CF:

- Excessive salt and sweat loss
- Portacath (avoid contact sports / martial arts)
- Exercise induced hypoxia (oxygen saturations <90%)
- Cough / Dyspnoea
- Bronchoconstriction
- Pneumothorax (Scuba diving may increase the risk of pneumothorax)
- Haemoptysis
- CFRD
- Liver disease & low bone density (avoid contact sports / martial arts)

Exercise plans should include components of aerobic, strengthening and flexibility exercise which should be moderate to vigorous activity, in addition to the child's normal habitual physical activity. The aim is for exercise to be consistent and varied, fit into family life with the aim of becoming a habit.

Whilst Exercise Guidelines recommend 60 mins a day of moderate to vigorous exercise daily, experience tells us that many children and families find this hard to achieve. Local guidance is often 30 mins a day getting 'hot sweaty and out of breath'. Web based logs, online classes and resources may be useful for motivating certain age-groups and activity sensors can give the physio more information (energy expenditure, step count and time spent in different intensities) when assessing exercise and making recommendations.

With the advent of modulator therapy children with CF are likely to have less severe lung disease and so the role of exercise to maximise function is being explored more. Research in the adult population has shown that people with CF regularly substitute exercise for ACT and there is research taking place exploring whether exercise could replace ACT. However, at the time of writing there is no long-term evidence establishing whether exercise can replace ACT or the optimal type/frequency/intensity/duration which would be needed, so this is not something we recommend.

6.16b 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 percussion as well as infant positive expiratory pressure (iPEP), assisted autogenic drainage (AAD) and age appropriate exercise.
- **From 2 years and upwards** – When the child is able, introduce blowing games, bubble PEP and forced Expiration Technique (FET) "huffing" with the aim to progress to Active Cycle of Breathing Technique (ACBT) when able. Incorporate physical activity in the session. Variety is important in this age group to aid adherence. Positive Expiratory Pressure (PEP) and other oscillating PEP devices may be introduced as indicated.
- **From 8 years** – Encourage more independent treatments using a full variety of airway clearance devices and techniques as appropriate (with family support /supervision). The frequency and duration of ACT will alter depending on infective exacerbations, severity of disease and individual circumstances. In general, airway clearance is performed twice a day for 10-15 minutes following assessment by the physiotherapist.

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 an 80cm 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. Careful consideration should be given to age appropriate blowing toys, cost and infection control (i.e., can blowing toys be completely dismantled, washed, disinfected and air dried or are single use and disposed of?).
- **Positive Expiratory Pressure** (PEP) – Provides resistance to expiration through a mouthpiece (with nose clip) 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 (may be combined with assisted huffing).
- **High Pressure PEP** – 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®, Acapella®** and **Aerobika®**). Create positive expiratory pressure and oscillation on exhalation to prevent premature airway closure, mobilise secretions, improve airway patency and reduce sputum viscosity.
- **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. 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 manufacturer's guidelines). See also Appendix 9 for practical advice.

Further information regarding use and evidence for the above ACT's please refer to Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis, 4th edition November 2020.

Also see the following link for patient information leaflets on individual techniques:

https://www.cysticfibrosis.org.uk/the-work-we-do/resources-for-cf-professionals/supporting-clinicians/resources-for-clinicians/physiotherapy-resources

For all equipment queries please contact NebPhysioEquipment@rbht.nhs.uk who will be pleased to help you.

The timing of inhaled medication around airway clearance is important to optimise effectiveness:

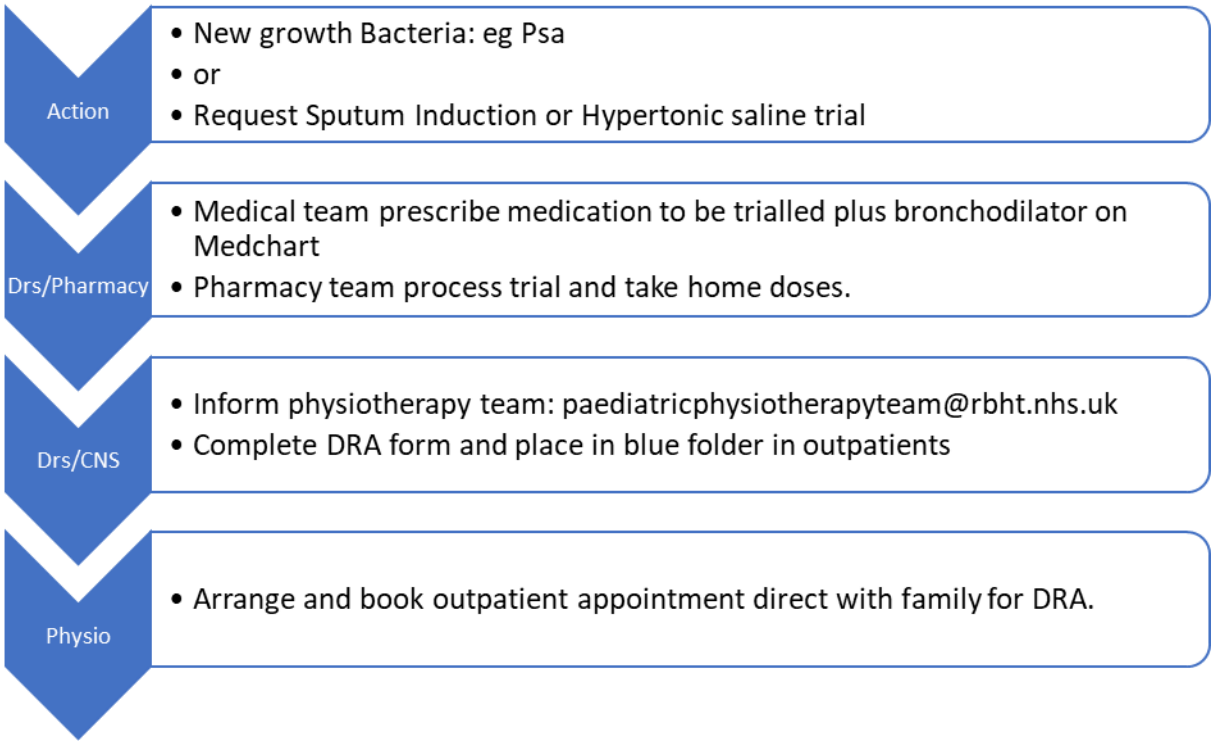
- Bronchodilators - pre-physiotherapy if necessary and benefit shown. No need to do this routinely 10-15 mins before physiotherapy, effect can be quite fast so quicker for child if use it at time of physiotherapy session.
- Hypertonic Saline - Immediately pre-physiotherapy but post bronchodilator. Can 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).
- RhDNase – Timing is decided on an individual basis. In most cases it is given at least 30 mins pre-physiotherapy. Cochrane review states "RhDNase can be administered before or after ACT to suit the individual, although in children with well-preserved lung function FEF_{25} was improved if RhDNase was given prior to ACT. If RhDNase is given before ACT it should be a longer time interval than immediately before ACT" We believe it is best given 30 mins pre-physiotherapy. In exceptional circumstances, it may be given pre-bed if the child is having difficulty fitting in all their therapies – this is a consultant or senior physiotherapist decision; parents must monitor for excessive overnight cough.
- 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.

6.16c Inhaled Drug Response Assessment (bronchoconstrictor challenge)

See appendix 7 for details of Drug Response Assessment and pass/fail criteria.

Process for requesting DRA



DRA form will be online soon.

For inhaled antibiotics (nebulised and dry powder) and hypertonic saline the child must always have a drug response assessment (DRA) to detect any bronchoconstriction when the 1st dose is given. This should be done in hospital and requires the patient to have auscultation and SpO_2 monitoring before, after and throughout the test and perform pre and post dose spirometry where age appropriate. If the patient already always takes an inhaled bronchodilator before physiotherapy, then this should be taken before the baseline lung function.

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

- We intend to use salbutamol before **all** doses of hypertonic saline, which can be given by a spacer device.

- We will only use salbutamol with nebulised antibiotics if they fail the challenge. Nebulised salbutamol can be added to colistin (but **not** tobramycin or aztreonam). Otherwise, it should be given beforehand via a spacer.
- If they always take salbutamol before physiotherapy, they should still do this, and it will still be active at the time they take the inhaled antibiotic which is done after physiotherapy.

During the DRA appointment the clinician will provide the patient and family with important information (including device education and cleaning, the best inhalation technique, how to reconstitute where required, storage, timing around airway clearance, adverse reactions to be aware of and important safety netting advice).

We do not need to repeat a DRA if a child is changing a tobramycin nebuliser generic brand, only if the drug concentration is changing.

6.16d Nebulisers

Nebuliser systems available include Respironics Side Stream, Pari Sprint, Pari eFlow Rapid® and I-neb®.

The I-neb® can be obtained if Promixin is prescribed and is a breath actuated device and only emits aerosol on inspiration (it is only appropriate if the child is able to use a mouthpiece). The breathing modes include tidal breathing mode and target inhalation mode which reduces nebulisation time (not to be used if FEV_1 is <1 litre).

- Once Promixin has been dispensed (the box of Promixin will contain a disc to make the I-neb work), the patient should contact Bionical solutions limited (+44 (0) 330 808 8668) and a member of their team will arrange to visit the patient at home. They will personally deliver the device, teach 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**.** Patients that no longer require Promixin may keep their I-neb and discs for use with hypertonic saline and dornase alfa can be provided by the hospital. However, in this situation if the I-neb breaks it cannot be replaced.

- **NOTE - 1 MU colistin in I-neb ® delivers equivalent of 2MU via conventional nebuliser.**

Grey latched chamber -	Promixin, bronchodilators (1ml fill volume)
Green latched chamber -	Dornase alfa (1ml fill volume)
Lilac latched chamber -	Tobramycin and hypertonic saline. As the chamber takes a max of 2.5 mls, the dose must be repeated to give the standard 4 or 5 mls tobramycin and 4 mls hypertonic saline. NOTE medication given via the lilac chamber will need to be nebulised twice to achieve one dose – see table below.

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). However, in our experience we note that children under 5 years of age poorly tolerate nebulised tobramycin via a 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 8).

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/4 or 5 mls and hypertonic saline 7%/4mLs can be nebulised through the I-neb®.
* This is a lilac coloured flap that covers the disc containing the drug when giving tobramycin.
** Data on file (Profile Pharma)
The Pari eFlow® rapid uses touch spray vibrating mesh technology and reduces inhalation time by 50% compared to the Pari LC Plus®

Drugs & their nebulisers –

DRUG	**Mixed with**	**Device**			**Exhaust Filter**	**Timing with ACT**
		I-neb	**e-Flow ® Rapid**	**Jet *e.g.,* Pari Sprint, Sidestream**	*NB filter only with e-flow or conventional*	
Amikacin	250mg: 1ml of 250mg/ml amikacin add 2ml 0.9% saline 500mg: 2ml 250mg/ml amikacin add 1ml 0.9% saline	no	no	Yes**	yes	post
Amphotericin	Dilution: 50 mg in 10ml of	no	no	yes**	yes	post

DRUG	Mixed with	Device			Exhaust Filter	Timing with ACT
(Fungizone)	water for injection. Withdraw required dose and further dilute with water to a minimum volume of 3ml for nebulisation.					
(Aztreonam Lysine) Cayston	Comes with own saline (1ml 0.17%)	no	yes- special Altera chamber - nebulises dry	no	yes	post
Ceftazidime	1 gm in 3ml water for injection	no	no	yes **	yes	post
Colomycin (Colistin)	3ml 0.9% saline	no	yes	yes**	yes	post
Dornase alfa	n/a	yes- **green**	yes	Yes*	no	>30 minutes pre ACT or on discussion with the physiotherapist
Promixin (Colistin)	0.5Mu: 2ml 0.9% saline, remove 1 ml 1Mu: 1ml 0.9% saline	yes - **grey**	no	no	n/a	post
Hypertonic saline 3% 6% 7%	n/a	yes- **lilac** x 2 fills per dose	yes	Yes *	no	directly pre or during
Meropenem (From IV solution)	10ml 0.9% saline into 500mg vial	no	no	Yes**	yes	post

DRUG	Mixed with	Device			Exhaust Filter	Timing with ACT
	125mg = 2.5mls 250mg = 5mls					
Tobramycin - 300mg/4ml e.g., Bramitob	n/a	yes, **lilac** x 2 fills per dose	Yes (but not recommended in <5yrs)	yes**	yes	post
Tobramycin - 300mg/5ml e.g., TOBI	n/a	yes **lilac** x 2 fills per dose	Yes (but not recommended in <5yrs)	yes **	yes	post
Vancomycin	Reconstitute according to manufacturer's instruction (consider displacement volume). Draw up required dose and make up to a total of 4ml with sodium chloride 0.9%.	no	no	yes	yes	post

Cleaning and disinfection of the nebuliser devices is vitally important (follow manufacturer's advice). See also Appendix 9 for practical 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 and when appropriate a new plan is provided, as well as exercise and progression of treatment where appropriate. Liaison with homecare physiotherapy service occurs as required.

6.16e Dry powder inhaled antibiotics (see also section 6.2a 6.III).

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 6.16c), 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 not closer than 6 hours apart. As with most inhaled antibiotics it is recommended they are taken after airway clearance. 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:
https://www.medicines.org.uk/emc/files/pil.4757.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™ – 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. Wash mouth out after use to minimise risk of developing oral fungal infection.

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 6.16c), 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 fat end goes in first and press the plunger slowly. There is a new capsule coating, so they are supposed to no longer break.

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_1.

6.16f Induced sputum (IS)
(See appendix 10 for protocol)

Isolation of bacteria from the lower airways is difficult in children who do not cough up sputum. Our data demonstrate that sputum induction resulted in 8 times more positive bacterial cultures than same day cough swab. It was also 3 times more likely than a cough swab to confirm failed eradication following a new/first growth of *Pseudomonas aeruginosa.* Therefore, sputum induction is recommended for those who have declining lung function, recurrent coughs and multiple courses of oral antibiotics and are non-productive of sputum, with no significant bacterial growth, before considering a bronchoscopy under general anaesthesia.

We also consider it for children who have previously grown bacteria only on bronchoscopy following eradication treatment when the child is not productive of sputum. In this case we perform it 2 weeks after the antibiotic eradication period ends.

We routinely perform sputum induction on all non-sputum producing children after eradication of a new *P aeruginosa* growth. The IS should be booked at the time of starting eradication therapy on ICE. We will also check for eradication of Aspergillus infection.

Induced sputum will also be done at the start of an admission in a non-sputum producer who has grown nothing recently and is being treated with IV cefuroxime as a single agent. We will not rely on a cough swab.

If the child is already on hypertonic saline and <u>able to expectorate</u>, we will provide a virtual appointment to assess them taking their hypertonic nebuliser and completing airway clearance at home. We will coach them to produce a sputum sample to send in.

If the child is <u>unable to expectorate</u> then we will bring them into the hospital for IS. If they are not already taking nebulised hypertonic saline, then we will perform an induced sputum using a jet style device. If they are already taking hypertonic saline, then we will do the IS using an ultrasonic nebuliser device – see appendix 10 - sputum induction protocol and flowchart - deciding between hospital and home samples.

An appointment for sputum induction in the hospital takes approximately 1 hour. It involves the child inhaling 7% hypertonic saline for 15 minutes via a jet or 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. See appendix 10.

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.

6.17 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 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.

It is extremely unusual for us to have a child with CF on home oxygen (we have not had anyone for many years). Oxygen prescription submission is managed by the RBH oxygen service. Their contact details are oxygen@rbht.nhs.uk or bleep 7755 or ext. 84451. An ICE request must be filled in online in the 'Rehabs and Therapies' section. Using ICE to submit a referral does not change the requirement, where applicable, to complete an IHORM-HOCF at the time of the referral. Completed IHORM-HOCFs can either be uploaded by the referrer to EPR or emailed to the Brompton Home Oxygen Service at either oxygen@rbht.nhs.uk or rbh-tr.oxygenrbh@nhs.net. Both forms can be found on the Intranet at the following web page: https://www2.rbht.nhs.uk/services/respmed/oxygen/home-oxygen-prescription-rbh/.

6.18 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 now very rare 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 Cochrane review demonstrated few studies but some benefits especially in dyspnoea. In our experience there are some children with worsening disease (in the absence of CO_2

retention) who benefit from nocturnal respiratory support as it improves daytime quality of life (improved sputum clearance, exercise tolerance and decreased fatigue).

- More commonly, mechanical positive pressure can be a useful addition to airway clearance, the principle being that positive pressure gets air 'behind the sputum', aiding its clearance and supporting the patient's work of breathing. This can be achieved by using the BIRD (or similar inspiratory positive pressure device). We are no longer able to use the NIPPV device (iSleep®) for this purpose.

- If the patient has had a pneumothorax, then caution is required before restarting NIPPV. If the person is dependent on it due to severe disease, then clearly it will need to restart immediately but see if a reduced pressure can be used. When being used as a physiotherapy adjunct, use reduced pressure for 2-3 months if its use still required.

7. Gastrointestinal & nutritional care

7.1 Nutritional care & assessment

The aim of nutrition support 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.

It is expected that generally children eat well and should be 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, low mood/depression, gastrointestinal disturbances (*i.e.*, constipation, DIOS, abdominal distension or pain), a dislike of high-energy foods, and/or some psychological/behavioural factors.

Children and families should be encouraged to follow a balanced and varied diet, but with added energy. This helps to promote normal eating behaviour and avoids feeding difficulties at a later stage. Nutritional care plans are individually tailored and include practical suggestions on how to increase energy intake and meet these high requirements. This may include food fortification advice with the addition of fats (aiming for healthy fats as much as possible *e.g.*, oil, avocado, nut butters etc.) or encouraging additional protein. This will help to increase the caloric density of meals. Use of prescribed oral supplements can be used if required.

As well as a high calorie diet, it is important to consider the need for additional fat-soluble vitamins, fluid and salt.

Malabsorption of fat-soluble vitamins (A, D, E & K) is common in CF.

- **All** children are supplemented from diagnosis, with the aim of achieving normal fat-soluble vitamin status.
- Pancreatic insufficient patients will always require fat soluble vitamins and remain on them life-long. They should be taken at the same time as PERT.
- Pancreatic sufficient patients are recommended to have fat soluble vitamins until the age of 5 so are also prescribed DEKAs Plus. From that point, as they still require vitamin D and K, due to their effect on bone metabolism, the easiest way to do this is by continuing DEKAs.

Vitamin levels are tested at annual assessment and dosages adjusted as necessary. (See section 11.2b on vitamin preparations). Be sure that pancreatic sufficient patients do not have high levels of vitamins A&E. Note that we are getting high levels in some patients on Kaftrio, so results are being checked by the dietitians and pharmacists and dose adjustments made.

It is essential for all CF patients to remain well hydrated, so they are encouraged to drink at least their requirement of fluid, if not more, each day. This is particularly important during periods of hot weather in the UK, on holidays abroad in hot climates, and during exercise. It is recommended that salt is added to food routinely which is usually sufficient to replace additional losses. In some cases, salt supplements can be prescribed for patients with

particularly high needs or those who dislike salty foods. This will need to be adjusted in those on Kaftrio with a normal sweat chloride as supplements should not be needed.

Nutritional Assessment

A specialist Dietitian is available in CF clinic and children are reviewed on a regular basis. At each review the Dietitian will assess growth, calorie intake, enzyme dosage, and education will be provided as needed. All children must be weighed and measured at every clinic visit. Children under 1 are weighed naked and children over 1 are weighed in light clothing *i.e.,* removing jackets, jumpers and shoes. In addition, infants under 1 year should have their head circumference measured. This data should then be plotted on appropriate weight, height and BMI growth charts.

The aim should be for infants and children with CF to grow normally, with infants achieving weight and height centiles like the non-CF population by 2 years of age. For adolescents the aim should be a BMI at the 50th centile. Please note BMI should not be used as a one off in isolation in growing children, height and weight centiles trends should be assessed, as stunting can be masked.

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 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 difficulty regaining their birth weight, who are drifting across centiles in the early stages, and those who suffer with ongoing gastrointestinal issues.
- Children that cross centile lines in a downward trend. This can be an acute picture or a longer, and potentially less noticeable, chronic change.
- Children with a BMI of <25th centile should be considered 'at risk' of malnutrition, with attention paid to height and weight trends.

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

Nowadays malnutrition rarely presents as poor linear growth alone, therefore if children are identified with faltering growth on their height centile, they are referred to our endocrinologists Nicola Bridges or Saji Alexander for further investigation.

Children with unexplained faltering growth should have the following considered –

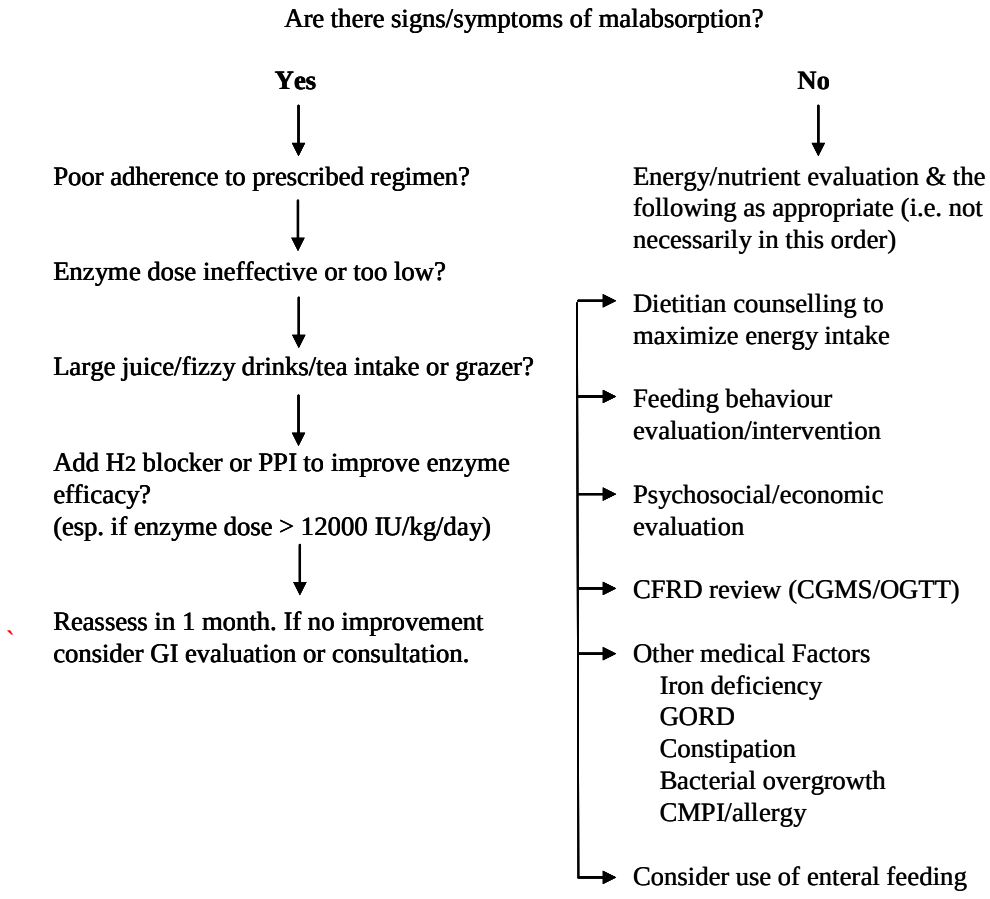
- Check for malabsorption *e.g.,* enzyme dosing and adherence, stool microscopy for fat (fat globules). Any child labelled 'pancreatic sufficient' should have faecal elastase checked again.
- Check calorie intake with food diary.
- Serum vitamins A, D & E.
- Urinary & serum electrolytes. A spot urine sodium of <20 mmol/L indicates a low total body sodium and requires correcting to support weight gain. This is not measured routinely in newborn infants up to 3 months of age as their urine sodium is often low. In this case if growth is a concern in infants, sodium supplements are started automatically.

- 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 gut surgery) must be excluded.
- Cow's milk allergy should also be considered in infants.
- Check psychological well-being.

Refeeding syndrome

If a child is admitted with very poor nutrition, care must be taken that once they start to feel better with treatment of their chest or abdominal symptoms, they increase their intake slowly, otherwise 'refeeding syndrome' can occur. This can also occur if they are enterally fed too quickly. The syndrome is seen typically when refeeding patients with anorexia nervosa and can include breathlessness due to impaired diaphragmatic contractility, oedema, ascites and heart failure; it is accompanied by hypophosphataemia, hypomagnesaemia and hypokalaemia. Good reference for refeeding is Sachs et al, Eating Disorders 2015;23:411-21.

Algorithm for weight loss or lack of weight gain



Adapted from Borowitz et al J Pediatr Gastroenterology 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 test is not affected if the children are already taking pancreatic enzymes. The sample should be sent to Biochemistry.

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 useful as an early indicator for the need to commence 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 months of age, 6 months and then at the 1st annual review. This may be repeated sooner if results are in mild to moderate range (*e.g.*,100-250) or if symptomatic. After one year, further repeats will only be done if clinically indicated, rather than routinely.

Requirement of PERT varies widely and should be assessed on an individual basis following dietary and symptom analysis. Abdominal symptoms and stool characteristics such as oily, floating, pale/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.

Note that the PERT requirement may reduce in children after starting CFTR modulators. Faecal elastase should be rechecked.

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 and 25,000 units.

Pancreatic enzymes should be taken with all meals, snacks and drinks containing fat and protein. Education on the amount of Creon taken with different foods is provided by the Dietitian. Some foods do not require enzyme supplementation. These are sugars/carbohydrate only foods:

- Fruit (except avocado) and vegetables
- Sugar, jam, honey, syrup
- Fruit juice, fizzy drinks, and squash

- Sorbet or fruit lollies
- Jelly and boiled sweets
- Juice-based supplements

Infants and children under the age of 3 are started on enteric-coated microspheres (Creon Micro). Creon Micro contains 5000IU lipase per Creon scoop. These are currently only available as a porcine base and hence there may need to be a discussion with families of certain cultures and religions. The granules are given on a spoon in a small amount of apple puree (just enough to suspend the granules in) at the start of feeding. Enzyme granules ***must not*** be mixed into a bottle formula or into a meal as the enzymes will be activated before they reach the small intestine. The enzymes can be denatured within the acidic stomach so become ineffective. In addition, enzyme granules are unpleasant to chew, can cause ulceration of the mouth and gums, and can deter children from eating. Parents are offered the switch to Creon 10000 IU capsules at the 1st annual assessment for practical reasons. In this case parents open the capsules onto the apple puree. One capsule is the equivalent to 2 scoops of Creon Micro.

It is recommended that parents follow the Department of Health guidelines when infants are commenced on solids. The Dietitian will offer individualised advice to parents to ensure that PERT doses are calculated correctly depending on what foods are offered. Parents will often require more frequent advice at this stage.

Between the ages of 2-5 years old children should be encouraged to learn to swallow capsules. They should be swallowed whole and are generally taken at the start of a meal. Although there is a lot of research into optimal timing of PERT none is conclusive. Enzymes can be taken at the beginning, during, or at the end of a meal. Enzymes are most effective for 20-30 minutes once taken, so ideally meals should be finished within this time. This is not practical for all children so splitting the dose of enzymes between the main course and the pudding can be more effective. It is important to have quick and easy access to enzymes for better adherence. For any children who are having difficulty swallowing capsules after the recommended age, a play therapy team referral for pill school may be useful, usually from the age of around 3 years.

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 and normal growth is achieved.

- Babies: 1/3 – 1/2 scoop increasing to 1-2 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

Some infants may become constipated, when commencing Creon therefore may require additional cooled boiled water or Dioralyte daily basis whilst establishing Creon dose to support bowel motions.

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 taking large numbers of capsules.

National guidelines advise against doses exceeding 10,000 IU lipase/kg. However, it is frequently observed that many infants and children require doses higher than this to control symptoms of malabsorption, especially during stages of accelerated growth *e.g.*, infancy and adolescence. When a child is on a particularly high dose, (*e.g.*, >15,000 IU lipase/kg/day) the Creon prescription and other routine clinical investigations should be reviewed 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 to reduce gastric acidity.

In the case of patients who are solely tube fed, although not licenced, Creon Micro can be flushed down their feeding tube. The tube must be well flushed to avoid blocking and degradation. Only tubes of 14FR or larger are suitable as granules will not pass easily through a smaller tube. If necessary, Creon micro can be dissolved in water and/or sodium bicarbonate (to be discussed with Doctor and Pharmacist). Pancrex V powder (scoop provided to measure dose) or Pancrex V capsules (open them and use the powder) can also be considered.

7.3 Salt & its supplementation

Patients with CF have a higher sodium requirement due to additional losses through sweat, especially in hot weather, exercise, periods of ill health and additional fluid loses such as diarrhoea and a high output stoma. They are susceptible to more rapidly depleting stores and therefore should be encouraged to include extra salt in their diet. Sodium is essential for growth and maintaining hydration. The current guidelines for Europe and the UK do not advise routine supplementation but encourage an individualised approach. The current recommendation is to give additional sodium during hot weather and exercise and should be considered for infants where growth is a concern. However, it is becoming more evident that some centres are using supplements as routine, including Australia and the USA. There is currently no evidence to support this although it has recently been shown to have a positive effect on catch up growth in young infants.

Infants are more susceptible to becoming sodium depleted due to the low sodium level in both breast milk (15mg/100ml, or 0.65mmol/100ml) and standard infant formula (17-24mg/100ml, 0.7-1mmol/100ml). It has been shown that young infants have a low clearance rate for sodium irrespective of their total body sodium or serum level and therefore testing urine sodium at an early age is a poor indicator of sodium status. Therefore, if growth becomes a concern then sodium should be supplemented regardless of urinary sodium level.

<u>Note that children starting Kaftrio may require a reduction in their salt supplement.</u>

- If Kaftrio has decreased sweat chloride to <30, then you should not need salt supplementation routinely. Extra salt on the food is also not indicated.
- If Cl is in the 30-60 range, then a reduction in salt supplementation is recommended but may still be needed in the summer.

Supplementation

The current recommendation for sodium supplementation is 1-2mmol/kg in paediatrics when required.

Breastfed infants

For breastfed babies it is preferable to give sodium supplements. This comes in the form of 1mmol/ml or 5mmol/ml solutions, although some high street pharmacists are using other strengths at times. It is most important that we know what strength sodium chloride solution has been prescribed and what has been dispensed and both the strength and dose should be included in clinic letters. It can be given directly into the mouth or mixed into milk/apple puree just before a feed. If the baby starts ivacaftor at 4 months of age, consider stopping sodium chloride supplements but check urine Na first.

Bottle fed infants

As the baby is used to drinking from a bottle then an oral rehydration solution such as Dioralyte can be used as first line. This is easier than giving sodium solution, more palatable, and gives the baby additional fluid. One sachet of Dioralyte makes up 200ml. This can be given as 100ml once, or twice a day, providing 6-12mmol sodium chloride respectively. This is usually sufficient in meeting the recommended dose in a young infant weighing around 3-5kg. Once made up, the Dioralyte solution can be kept for up to 24 hours in the fridge. It is often a concern that if a baby is drinking Dioralyte the milk consumption may reduce however this is rarely seen in practise and they will drink this in addition. Sodium solution can be used if Dioralyte is not tolerated. If the baby starts ivacaftor at 4 month of age, consider stopping dioralyte or NaCl supplements but check urine Na first.

Older infants

If a baby is weaning or eating small meals, then salt can be added to food. The amount of salt can be guided by the Dietitian but ~one sixth teaspoon salt is equivalent to 15mmol NaCl. If growth is a concern, then prescribing Dioralyte or sodium solution is a better option to ensure the intake is sufficient and consistent.

Children

Children should be encouraged to follow a salty diet as a part of their regular daily intake. This should include *naturally* salty foods within a healthy diet for example, ham, cheese, olives, bread, baked beans, tomato ketchup, marmite etc. and then foods with added salt *e.g.*, soups, crisps, pizza. As soon as children can swallow tablets then these can be used as well, for example Slow Sodium, which provides 10mmol sodium chloride per tablet. However, Dioralyte can be a better option as it also provides additional fluids.

For children who are particularly active, are very sweaty or simply dislike salty foods then routine salt supplements should be considered. Fluids should always be encouraged in tandem.

Holidays to a hot country or particularly hot weather in UK

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; 1-4 / day, age dependent). This is also necessary in very hot weather in the UK. See Appendix 14 for more information.

7.4 Oral nutritional support

There is a wide range of prescribable products available - largely drinks and fortifiers - for children with 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 in between mealtimes, or in the evening. Parents can use supplements creatively (*e.g.*, in cooking) to encourage intake and avoid taste fatigue. In our experience, short term use of supplements, with good adherence to the recommendations regarding these 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 Pro High Energy (SMA) • Infatrini (Nutricia) • Similac High Energy (Abbott) • Concentrated Standard infant formula – *must* be supervised by the Dietitian
	Paediatric	• Paediasure Plus & Paediasure Compact (Abbott) • Fortini & Fortini smoothies (Nutricia) • Frebini Energy (Fresenius Kabi)
	Adolescent	• Ensure Plus (Abbott) • Ensure TwoCal (Abbott) • Ensure Compact (Abbott) • Scandishake (Nutricia) • Calshake (Fresenius Kabi) • Enshake (Abbott) • Fortisip (Nutricia) • Fortisip Compact & Fortisip Compact Protein (Nutricia) • Fresubin Energy (Fresenius Kabi)
Juice Based Supplements	Paediatric	• Paediasure Plus Juce (Abbott)*
	Adolescents	• Ensure Plus Juce (Abbott)* • Fortijuice (Nutricia)*
Powder and liquid polymers to add to foods	Carbohydrate	• Maxijul (SHS)* • Polycal (Nutricia)*
	Fat emulsions	• Calogen (Nutricia) • Liquigen – MCT fat (Nutricia) * • Fresubin 5kcal shot (Fresenius)

	Mixed macronutrients	• Duocal (Nutricia) • Calogen Extra (Nutricia) • Procal Powder (Vitaflo) • Procal Shot (Vitaflo)

** DO NOT NEED ENZYMES*

7.5 Enteral nutritional support

Only a small number of patients will require supplementary feeding which will provide long term "intensive" nutritional support. Gastrostomies can be beneficial in stabilising and promoting weight recovery and preventing ongoing weight loss affecting linear growth. Discussions about the potential need and benefits of gastrostomy feeding should commence early to avoid the stigma of insertion being associated with nutritional 'failure'. We have found that the need for gastrostomies has fallen over the last decade. This is likely due to increased awareness of the importance of nutrition at diagnosis, and the implementation of the newborn screening programme.

A gastrostomy should be considered if there has been a progressive fall in weight on the growth chart despite the following:

- Intensive dietetic support with repeated attempts to improve dietary intake. This includes appropriate dietary modification and trials of 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 psychologist
- Exclusion of other conditions, especially CFRD and Pseudo-Bartter's syndrome.

Do not leave the decision over a gastrostomy too late in someone with poor nutrition and deteriorating lung function, otherwise the risk of the operation may become too high.

The following investigations should be carried out:

- CGMS
- Urinary sodium
- Serum electrolytes
- Thyroid function
- Coeliac screen: TTG (anti tissue transglutaminase) IgG & IgA; endomysial antibody. Ensure that the total serum IgG/IgA is known as well
- ESR
- Faecal calprotectin (plain container) *

***Faecal calprotectin** can indicate inflammatory bowel disease when significantly raised; if it is normal it is not IBD which is its main use. Levels can be raised in CF anyway, associated with pancreatic insufficiency, CFRD, and PPI use, but also due to CF enteropathy.

<50-75 mcg/g	definitely normal
<200	likely to be normal
>500 (esp. >1000)	could be IBD

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. Existing behavioural feeding difficulties, which are not addressed, may continue to impact on the young person's feeding even after a gastrostomy is placed.

Patients and parents should be introduced to the concept of a gastrostomy as a part of general nutrition support education in the early years. When the decision has been made to progress towards a gastrostomy it is important that families are educated on the potential effects. This includes the effect on growth, timely initiation of puberty, other contributing factors effecting the stress levels in a family, and overall health. Some children and parents find it useful to speak to a patient who already has a tube in place. The play therapy team have access to gastrostomy models which can be a helpful visual aid along with other written information. Body image can be a concern after placement of a gastrostomy, particularly in teenage girls. Early recognition of a distorted body image is essential, so that counselling can be arranged. It is critical however that a procedure for a gastrostomy is not left too late due to parental or professional procrastination, as the operation and general anaesthetic risk is increased markedly if the child is malnourished with a poor respiratory status.

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 done by Mr Simon Clarke (Consultant Paediatric Surgeon).

- To **organise** a gastrostomy, please contact the paediatric surgery secretary on 0203 315 8885.
- Also liaise with the Surgical Clinical Nurse Specialist at C&W on 0203 315 8627 or 0203 315 8000 bleep 4988; or via cw.gastrostomy@nhs.net who will assist with parent education.

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). Children with poor nutrition and suboptimal lung function 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 0203 315 8627 or 0203 315 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.
- 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

Each child is individually assessed, and the most appropriate feed is chosen to match their nutritional requirements. Only around 20% of the EAR should be given via the tube. Feeding regimens are frequently reviewed to ensure these fit within a patient's lifestyle. Gastrostomy feeds are usually given as a continuous infusion by a feeding pump for 8-10 hours overnight, aiming for a 1-2 hour break before physiotherapy in the morning. Oral intake is encouraged during the day. Occasionally additional feeds are used to supplement daytime intake, particularly during acute illness. Allowing a night off each week can help with compliance, especially in teenagers.

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

If there continues to be ongoing issues with malabsorption and poor weight gain, then a feed containing hydrolysed protein and a fat source from medium chain triglycerides (MCT) will be considered. Due to the nature of these feeds, it is possible that patients will require a lower dose of enzymes but is not always the case. The Dietitian will advise on enzyme dosing for these feeds. Fibre containing feeds are not frequently used in CF patients.

Most feeds come in 'ready to hang' bottles and are therefore 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.

	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 Dietetic supervision)
	Standard Infant formula	✓			0.67 kcal/ml
	Neocate (Nutricia)	✓			0.68 kcal/ml
	Pepti- Junior (Cow & Gate)			✓	0.66 kcal/ml
	SMA High Energy (SMA)	✓			1.0 kcal/ml
	Infatrini (Nutricia) / Similac High Energy (Abbott)	✓			1.0 kcal/ml
Paediatric Feeds (8-20 kg or >1 yr of age)	Paediasure (Abbott)	✓			1.0 kcal/ml
	Paediasure Plus (Abbott)	✓			1.5 kcal/ml
	Nutrini Energy (Nutricia)	✓			1.5 kcal/ml

	Peptamen Junior Advance (Nestle)			✓	1.5 kcal/ml
	Nutrini Peptisorb			✓	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
	Fortisip Compact (Nutricia) / Ensure Compact (Abbott)	✓			2.4 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 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.

7.6 Promoting healthy feeding behaviour

Ensuring adequate nutrition for a child with CF can be very challenging and often leads to feeding difficulties or unhealthy relationship with food. This not only has an impact clinically but can also be very difficult for families to manage. There are many reasons for this, but often include the higher incidence of reflux, taking enzymes and other medicines with meals, and the ongoing emphasis to optimise nutrition and fluid intake. It is therefore best to encourage children and their families to develop a relaxed and positive attitude towards food and nutrition as much as possible.

For most parents weaning infants onto solid food is an enjoyable experience. However, they can often require extra support and advice at this stage. The Department of Health guidelines for weaning are appropriate for children with CF. The dietitian can offer individualised advice to ensure that enzymes are dosed correctly.

At any time of their lives, most children's appetite and intake can vary from time to time. This is typical in a child's development and we advise the same parental guidance about managing mealtimes and snacks as for any other child. While nutrition is very important, families are encouraged to make mealtimes as ordinary as possible without focusing on the type or amount of food consumed. If a parent is concerned for any reason, the team can give individualised suggestions as to how to minimise anxiety at mealtimes for them and their child. We encourage families to discuss this with their child's dietitian, clinical nurse specialist or paediatrician as soon as possible to ensure behaviours do not become a long term problem. Suggestions will be implemented and if the challenges persist a referral to the paediatric psychology or other (*e.g.*, feeding) team may be discussed and/or advised.

The following principles are encouraged to promote healthy feeding behaviour. However, if parents have a style of parenting which does not follow the below, this is fine unless nutrition of their child with CF presents as a problem to their general health and/or well-being:

- Adults and other family members modelling healthy eating and enjoyment of food, including eating socially - as a family or with peers/friends.
- Having a consistent approach from all adults involved with feeding a child.
- Creating a relaxed and enjoyable feeding environment *e.g*., avoiding distractions such as the television - if this appears to interfere with the child's feeding behaviour.
- Offer age appropriate portions and offering second helpings if desired.
- Giving *gentle* encouragement to eat and positive feedback for good behaviour.
- Try to ignore feeding behaviour that is not acceptable.
- Creating a structured meal and snack pattern appropriate to the child's age and lifestyle.
- Limiting mealtimes to a maximum of 30 minutes (meals that last longer than this rarely result in higher calorie consumption in the long run).
- Not offering alternative meals or snacks if that chosen (out of two options) is then refused, having been agreed on, prepared and presented.
- Engaging children at mealtimes (for example 'messy play', self-feeding and simple food preparation).

7.7 Gastro-oesophageal reflux & unsafe swallow

Gastro-oesophageal reflux (GOR) is common in infants with and without cystic fibrosis. It has a range of severities and most children will have fully grown out of it by 18 months of age; although symptoms will often have gone before this age, lessening from about 6 months. From our own data about 50% of infants will have GOR when measured by a dual probe 24-hour pH study at 4 months of age. Most will display some symptoms such as colic, posseting and effortless vomiting characteristically being able to feed straight afterwards, although reflux can be silent. In an infant without CF who is thriving, these symptoms may not be treated, or a simple milk thickener may be used. In CF there is some concern that GOR may have a negative impact on lung health, with possible aspiration so we have a low threshold to treat with an antacid, using a proton pump inhibitor (PPI) as a first line rather than thickeners. Infants that have evidence of discomfort especially with back arching should definitely be treated. Cow's milk protein intolerance or allergy can be associated with GOR in infancy and must not be forgotten in the face of severe symptoms, refusal to feed or faltering growth. Some children with CF do not grow out of their GOR or may develop it again later in life especially if they have worsening of their lung symptoms. It should also be considered as a potential reason for unexplained deterioration in lung function. Some children will complain of "sicky burps" or heartburn, a month of high dose PPI is recommended before dropping down to a single maintenance dose, usually in the morning to allow for some natural acidity to return to the gut overnight.

We try and avoid long term PPIs as there is an association (not necessarily causal) with hospitalisations and pulmonary exacerbations. At annual assessment, the need for PPI should always be reviewed, with a view to stopping.

There are no research proven motility drugs for use in GOR, but we occasionally use erythromycin if a PPI is not working for its prokinetic action. In the face of continued symptoms despite treatment, further investigation may include a milk scan to look for aspiration and/or a barium meal to check the anatomy of the stomach outlet prior to

considering a fundoplication. A pH study or impedance study are also useful and maybe a useful opportunistic investigation to do in conjunction with bronchoscopy.
We no longer screen all newly diagnosed infants with a pH study at 3 months. However, if we repeatedly grow coliforms (e.g., Enterobacter, Escherichia, Klebsiella, Citrobacter), we will assume the child has reflux, treat accordingly and consider a pH study.

Unsafe swallow – we have a few infants with obvious symptoms on drinking (cough, splutter, choking), and some with silent aspiration (asymptomatic on drinking). Unsafe swallow with aspiration of fluids is something to be considered in an infant with frequent symptoms or infections. When indicated we refer to our Speech & Language Team for a clinical assessment, and some will have a video fluoroscopy. Management is with thickened fluids and other techniques e.g., pacing (slowing down feeding), position etc.

7.8 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. With the introduction of CFTR modulators the incidence of DIOS is expected to go down with restoration of CFTR function in the gut leading to some normalisation of the motility and electrolyte balance. The pathophysiology is not fully understood, but there are often multiple contributory factors including:

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

Viscid muco-faeculent material accumulates in the terminal ileum / caecum usually leading to partial obstruction (now called “incomplete or impending” DIOS) with pain often 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). Bowel motion history can be inaccurate or misleading.
Important features that increase suspicion of DIOS are:

- Acute periumbilical or right lower quadrant abdominal pain
- Vomiting
- Palpable faecal mass in right lower quadrant
- Previous DIOS Complete DIOS is when there is total bowel obstruction characterised by abdominal distension, pain (often colicky), fluid levels on AXR and vomiting, usually bilious

Differential diagnosis
Constipation (commonest), adhesions post abdominal surgery, appendicitis, intussusception, volvulus, fibrosing colonopathy (extremely rare), biliary tract or gallbladder disease, acute pancreatitis, urinary tract infection, inflammatory bowel disease (stool calprotectin and history of fissures, blood or mouth ulcers may help with this differential).

Complete DIOS is rare in children, but a surgical opinion should be sought early if there is any doubt about the differential (e.g., risk of adhesions if previous surgery).

Investigations

- A good history and abdominal examination are often sufficient to diagnose DIOS.
- A plain abdominal x-ray (AXR) may be needed to diagnose DIOS or constipation, radiation dose is up to 20x that of a CXR and they should be used sparingly. Faecal loading throughout the colon, especially in the right iliac fossa suggest DIOS. Intestinal fluid levels confirm severe DIOS with obstruction; the differential diagnosis of a surgical cause of obstruction must always be considered. If there if are doubts over the cause of abdominal pain, the following may be helpful:
- WBC, amylase, liver function tests, ESR, CRP.
- Urinalysis
- Abdominal ultrasound.
- Barium /gastrografin enema - by specialist radiologist can diagnose and help treatment at same time.

Management of DIOS

1. Acute management

   A stepwise process will always include adequate hydration.

A. **Incomplete or Impending DIOS – Mild**

i. Ensure:

- Rehydration - patient must be well hydrated before and during treatment.
- Adequate salt replacement to help terminal ileum absorption of bile acids and correct any bowel CFTR electrolyte imbalance that may be implicated in DIOS.
- PERT therapy is reviewed and adjusted if needed.

ii. **Movicol**

The paediatric preparation is used up to 12 years old. Doses are age dependent, usually starting at 1-2 sachets daily. See formulary 11.2e.

iii. **Oral N-acetylcysteine-** a disulphide bond breaker, comes in sachets containing granules (200mg – dissolved in water, orange flavoured). There are also 600mg capsules, 600mg tablets, and 600mg effervescent tablets available. The 200mg/ml injection can be given orally but is usually only used in the neonatal setting and should be mixed with water to a concentration of 50mg/ml (orange or blackcurrant juice or cola may be used as diluent to mask the taste).

Oral gastrografin

Hydration is very important if gastrografin is used as it is highly osmotic. This is often done as an in-patient – for first doses and especially in the more severe cases when IV fluids may be required. Be particularly careful in babies & infants who can easily become dehydrated. See formulary 11.2e.

- Use for up to 3 days if no response in first 24 hours but not if symptoms worsen.
- Follow up with Movicol (paediatric if <12 yrs) for several weeks and review chronic management below.
- *Contraindicated if complete bowel obstruction*

A. Incomplete or Impending DIOS – Severe

- **Klean-Prep**
- Admit patient.
- Aim is to take solution until clear fluid is passed PR. See formulary 11.2e.
- NG tube is usually required as volume is so large but occasionally some patients will prefer to drink it (more palatable if cool).
- No food in 2 hours before the treatment and during the 4 hours of Klean Prep to be able to assess for clear fluid being passed.
- Beware hypoglycaemia and electrolyte imbalance
- Where Klean-Prep is not available **Moviprep** may be used in its place. A litre of Moviprep consists of one 'sachet A' and one 'sachet B' dissolved together in water to make one litre of solution. ONE Moviprep (sachet A + B contains 100g Macrogol 3350) is roughly equivalent to TWO Klean-Prep (each sachet contains 59g Macrogol 3350).

B. Complete DIOS – severe

If there is complete obstruction (e.g., bilious vomiting) an NG tube is needed to empty the stomach and prevent bilious aspiration, and IV fluids are given (‘drip and suck’). An early specialist opinion from gastroenterologist or surgeon may be needed, always beware of other causes of bowel obstruction or an acute abdomen.

- **Rectal gastrografin.** Same dose as oral, diluted as per formulary 11.2e. Consider rectal gastrografin if oral administration is not possible or if there is vomiting due to obstruction. This is rarely used and is a last resort. It can be administered **under radiological guidance to achieve a guided approach**. Watch for dehydration, a plain AXR at 1 hour may be required to exclude massive dilation. If the latter is present, urgent referral to a paediatric surgeon is required. Other treatments
- **Picolax** may be used as a first line instead of gastrografin
- Colonoscopy or surgery is rarely required although is indicated where above medical management has failed. May involve laparotomy and enterostomy or even bowel resection.

B. <u>Chronic (management after an acute event)</u>

The onset of DIOS may be indolent with just intermittent abdominal colicky pain, some anorexia and palpable right iliac fossa mass. Laxatives e.g., Movicol or occasionally lactulose in a young child should be continued for several months post DIOS. See Formulary 11.2f. Make sure child has been reviewed by a dietitian.
• Avoid dehydration - ensure adequate fluid & salt intake.
• Check dose / compliance / timing of enzyme supplements.
• If ongoing malabsorption is documented, consider starting omeprazole.
• Diet – ensure adequate dietary roughage.
• Ensure patient has well established toilet routine (try to go after meals), even at school.
• Movicol (Paediatric if < 12 yrs) is first line treatment, lactulose may help.
• In some children, oral N-acetylcysteine may help, especially in settling abdominal pain.

If continuing problems refer to Dr Krish Soondrum (who does a ward round on alternate Wednesday mornings on Rose Ward) or Dr Anthi Thangarajah who comes on alternate

Thursday mornings; or one of the GI consultants at Chelsea and Westminster Hospital in clinic.

Constipation

If severe should be considered as part of DIOS spectrum. However, beware of increasing enzyme doses when all that is needed is simple childhood constipation treatment. The main difference from DIOS is that constipation tends to be limited to rectum, so faecal masses are only felt in the left iliac fossa. Stool is more likely to be hard and pellet like or even painful to pass. This is likely to become more of a problem than DIOS as CFTR modulators are now in widespread use.

Treatment:
- Ensure adequate fluid intake.
- Movicol (Paediatric if <12yr) or lactulose may be used (see formulary 11.2f).
- Movicol dose can be adjusted up and down to produce regular soft stools.
- Lactulose can cause stomach cramps and flatulence in large doses.

7.9 Liver disease

The reported prevalence of liver disease in CF varies according to the definitions used. Liver involvement in CF is very common, but clinically important cirrhosis affects between 20-30% of adult CF patients and associated portal hypertension affects 5-10%. Symptomatic liver disease is reported as the cause of death in only 2.5% 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, for example α1-antitrypsin Z allele heterozygotes have a 7-fold increased risk of cirrhosis.

There is a wide spectrum of hepatobiliary complications arising in CF patients. This includes steatosis and focal or multilobular biliary cirrhosis, neonatal cholestasis in infancy (conjugated hyperbilirubinaemia secondary to bile duct obstruction), gallstones and cholecystitis in later childhood and abnormally raised transaminases. Intermittently raised liver transaminases are extremely common, this is observed in nearly all children with CF by the time they reach adulthood and doesn't always correlate with the presence or severity of CF related liver disease.

Steatosis (Fatty liver)

This is a relatively common CF finding, detected in 23-75% of patients on liver ultrasound. The pathogenesis is unclear, although it has been suggested that it arises secondary to fatty acid, choline or carnitine deficiency, or insulin resistance. Its natural history is still uncertain and the frequency of progression to cirrhosis is unknown. Guidance from King's College Hospital (Specialist paediatric liver unit) is that in the absence of hepato- or splenomegaly, and with normal liver function, they would not start ursodeoxycholic acid for steatosis alone but would repeat the ultrasound in 1 year. It is said that steatosis is not a biliary problem that would respond to URSO, and it is not a precursor of typical cirrhotic CF liver disease.

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. Other indications for ultrasound are persistently raised transaminases on 3 consecutive measures over 12 months, clinical hepatomegaly or clinical splenomegaly.
- Liver function tests (transaminases) have a poor sensitivity and specificity. Consider drug causes – discuss with the paediatric pharmacy team at the earliest opportunity.
- Prolonged prothrombin time (although more likely to be due to malabsorption of vitamin K than liver disease).

The liver ultrasound scan at annual assessment is now reported in a standardised manner and includes a measure of liver stiffness known as 'elastography'. The speed of sound travelling through the liver varies with liver disease with increasing sheer wave velocities representing increasing degrees of fibrosis. Sheer wave velocities are grouped into 4 classes via the Metavir system with each score representing worsening fibrosis. As with many quantitative imaging techniques, sheer wave elastography has yet to be properly validated in children and in CF and has the potential for significant inter-operator variability. It is telling that a Metavir stage 1 score correlates to normal-mild disease (i.e., there is no true 'normal' value per se). As such, single measurements should not be given too much weight clinically, but a trend of increasing measurements over time should prompt further investigation. It is also worth noting that liver disease is rarely homogeneous and where there is doubt, a measure of reliability is stored on PACS. If in doubt, please discuss with radiology or at the Wednesday lunchtime MDT as there is a role for MRI in certain cases.

Liver fibrosis Staging	Metavir Score	Sheer wave velocity (m/s)
Normal-Mild	F1	1.35-1.66
Mild-Moderate	F2	1.66-1.77
Moderate-Severe	F3	1.77-1.99
Cirrhosis	F4	>1.99

From GE's white paper on liver elastography using the GE LogiQ E10 – the machine used at RBH.

Standard treatment

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

- Ursodeoxycholic acid. This increases bile flow. It is well tolerated with main side effect of diarrhoea; in which case the dose is reduced. Ursodeoxycholic acid reverses markers of CF liver disease but it is unclear whether it can delay or reverse fibrosis. Doses should be reviewed regularly and optimised to 10-15mg/kg twice daily, particularly in cases where there is significant CF liver disease.

- We use Paravit-CF routinely for anyone with significant liver disease (which for these purposes we define as anyone on ursodeoxycholic acid) instead of DEKAs Plus, as it contains enough vitamin K so we do not need to prescribe extra vitamin K on its own (see section 11.2b).
- If there is significant abnormal clotting with a prolonged prothrombin time, extra vitamin K (menadiol or phytomenadione) may be needed. Occasionally 2 IV stat doses are required, and additional IV cover might be necessary at the time of surgical procedures.
- Platelet transfusion may be required to cover a surgical procedure if significant thrombocytopaenia. General guide is not needed >30-50 $x10^9$/L but consult with haematologist on each individual basis.
- Avoid aspirin and NSAIDs in those with documented cirrhosis.
- Care with drug therapy, including fusidic acid, minocycline, rifampicin, azithromycin, itraconazole, voriconazole, posaconazole and CFTR modulators (e.g., ivacaftor, Orkambi, Symkevi, Kaftrio). If in doubt consult with BNFc and a pharmacist.

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.
- Dr Marianne Samyn or Dr Tassos Grammatikopoulos at King's College Hospital for children with significant liver disease - 020 3299 5614 (or secretary 020 3299 1162).
- Dr Fuman Verma is the adult CF gastroenterology specialist who does a joint clinic once monthly at Chelsea and Westminster Hospital. 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 but consider in cases of severe liver disease.
  - Spontaneous bacterial peritonitis - rare in CF.
  - Hepatic encephalopathy - rare in CF.
  - Hepatocellular failure is rare but ominous.

- Jaundice - uncommon. Exclude other causes (sepsis, drug reaction, and haemolysis). Mildly elevated bilirubin on annual review bloods might be a sign of Gilbert's syndrome; if this is persistent, genetic testing is now available and can be undertaken if there are concerns.
- Gallstones - high prevalence but not always symptomatic in CF. If symptomatic, refer to surgeon for consideration of cholecystectomy.

7.10 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. We find ferritin levels are very often low as an isolated finding at annual review.

We have been 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. However, it seems that airway iron levels are not a function of serum iron, rather the leaky epithelium.

We therefore lowered our threshold for starting iron therapy**. We prescribe it if the MCV is low rather than just if Hb is reduced**. We still do not prescribe it at the earliest stages *i.e.,* when only the ferritin is reduced.

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. When iron deficiency anaemia and anaemia of chronic inflammation coexist, the conditions can have opposing influences and the ferritin and total iron binding capacity can be high, low or normal.

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 have seen some children with CF who have had significantly low MCV out of keeping with their Hb; in these cases, consider undiagnosed haemoglobinopathy. Ask about a family history and send haemoglobin electrophoresis and iron studies with repeat FBC prior to starting iron supplementation.

Also remember that iron deficiency anaemia may falsely elevate HbA1c making it even less useful in CFRD diagnosis and monitoring in patients with underlying iron deficiency.

We only measure Hb, MCV and ferritin to assess iron status at annual review.

Iron 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, lentils, beans, fortified cereals and eggs. Some parents may choose also to buy food supplements such as Spatone (iron rich water from Snowdonia). It is worth eating these with food rich in vitamin C as that can help iron absorption.

Remember that excessive consumption of cow's milk might impair iron absorption in children who are transitioning from breastmilk or infant formula after 12 months of life, particularly if they are not on a diversified solid diet that is rich in sources of iron and vitamin C.

	Iron deficiency			**Mixed**	**Iron malutilisation**
	Storage depletion	Iron deficient erythropoiesis	Iron deficiency anaemia	Iron deficiency anaemia and anaemia of chronic disease	Anaemia of chronic disease
Iron stores					
Serum ferritin	↓	↓	↓	↓↑ or N	N or ↑
Transport iron / iron supply					
Hypochromic red cells	N	↑	↑	N or ↑	N or ↑
Functional iron					
Hb	N	N	↓	↓	↓
MCV	N	↓	↓	N or ↓	N or ↓
Approach to management	Increase dietary iron	Iron supplementation	Iron supplementation	Address underlying inflammation	

8. Other non-pulmonary complications of CF

8.1 Cystic Fibrosis-Related Diabetes

Contacts

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

Diabetes Nurse Specialist, Chelsea & Westminster Hospital
Ms Hannah Morrow
Ms Shivaani Kaushik

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 not common 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 type 2 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 <11.1 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 insulin deficiency in CF is thought to be related to the CFTR mutation affecting insulin secretion as well as inflammation and fibrosis of the pancreas. There is evidence that modulator therapy impacts insulin secretion. However, the impact on individual insulin requirements is less clear. There may be a reduction of insulin requirement over time, but this is not guaranteed.

The WHO 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 evidence of benefit from treatment of impaired glucose tolerance. Treatment is aimed at improving clinical status as well as reducing the risk of long term complications of diabetes. Although, most clinicians use these standard definitions for diabetes in CF -treatment may be given to individuals who do not meet the criteria for diabetes, because the clinical situation is different.

<u>Screening for abnormal glucose tolerance and diabetes in CF</u>

Available tests of glucose status in CF

- Continuous Glucose Monitoring System (CGMS)
- Intermittent glucose monitoring system – Flash glucose systems / Freestyle Libre
- Oral glucose tolerance test
- Random glucose tests

When to test for glucose status in CF:

Current CF Trust recommendation is for screening once yearly in all CF patients over 10 years. Our current policy is to routinely carry out **CGMS in 10 & 14 year olds,** around the time of their annual reviews and to screen with CGMS at other times based on clinical concerns. OGTT is only used if CGMS is refused or not possible. **Currently screening is routinely undertaken only in pancreatic insufficient patients**

Consider doing a CGMS in a child of any age if:

- There is poor weight or height gain or decline in lung function with no other obvious cause.
- Elevated random glucose levels are measured at any time. Formal assessment is required if there are repeated glucose levels >8.0 mmol/l or a single level >11.0 mmol/l.
- HbA1c on annual review or at other times **>6.5%** (IFCC HbA1c **>48** mmol/mol).
- Symptoms of hyperglycaemia, including increased thirst, polyuria, blurred vision, constipation and candida infections.
- If there are documented hypoglycaemic episodes or symptoms suggesting this.

CGMS

Our first line option for CGM is flash glucose monitoring. There are several devices and more will be available soon; currently we use the Freestyle Libre.

How it works - A subcutaneous sensor measures the glucose in the interstitial fluid and gives a continuous profile of glucose levels for up to 14 days. The Libre is factory calibrated and does not require any finger prick calibrations. However, the Libre will need scanning with either a reader device or mobile phone at least every 8 hours to ensure 24 hours of data is collected (it automatically uploads with a smart phone). The data can then be seen immediately by the MDT via the online platform (Libreview) if scanned with a mobile phone. The equipment gives a profile and statistical breakdown of the glucose levels.

Advantages

- CGMS gives a better picture of glucose status in CF than either OGTT or random glucoses and 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

- CGMS needs to be used for sufficient time and can be influenced by food intake and activity at the time of the test.
- Clear guidelines as to when to treat based on CGMS are not available, however there is growing experience with the concept.
- The sensors are relatively expensive (£35-44 each).

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. Use Rapilose oral glucose tolerance test solution; 300 mls contains 75g anhydrous glucose (the adult dose) so adjust the volume depending on child's weight for those under 43Kg. Above 43Kg weight the dose is the full 300 mls (75g).

Lucozade is no longer useful as a substitute as its sugar content has been reduced.

- *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.

When to use an OGTT
- If it is not possible to get CGMS.
- 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.

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.

Glucose Control Test (GCT)

We are currently undertaking a trial of performing GCT in all children who are pancreatic insufficient ≥4yrs at annual assessment. This has advantages over the OGTT as children do not need to fast or have multiple blood samples taken. It involves having a glucose drink (Rapilose) and then having blood samples one hour afterwards. This is done alongside the other annual review bloods; there is no need for any additional blood tests. Data collection is ongoing; we hope that using GCT may help earlier detection of CFRD, and possibly reduce the need for routine CGMS (which is more invasive) for screening, at age 10 and 14, which is our current practice and will continue alongside the GCT for the time being.

Analysis of data to determine usefulness of the GCT and whether it should continue to be performed routinely at annual assessment will be undertaken during the lifespan of this guideline.

Profile of capillary glucose tests

Now we have the Libre, we do not often do a profile of capillary glucose levels. However, capillary glucose testing can be useful if the individual is an inpatient. Glucose levels may be elevated by infection and steroid treatment and high glucoses when admitted should be followed up, for example by CGMS when they are recovered or off steroids.

Testing should be before, and 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.

Interpretation of screening results:

CGMS
There are no fixed criteria for treatment with insulin based on CGMS. However, CGMS gives an accurate reflection of glucose levels during the test so it is acceptable to make management decisions based on this. For an individual with completely normal insulin secretion the CGMS will show that glucose is held steady within the normal range through the whole day, irrespective of the carbohydrate content of the food.

Our current management strategy is to divide CGMS results into 4 groups:

Diagnostic category	**CGMS values**	**Treatment**
CFRD	2 x peaks >11.1 mmol/l and >10% of time >7.8 mmol/l	Start insulin
Impaired glucose tolerance	No more than 1 peak >11.1 mmol/l and/or >10% of time >7.8 mmol/l	Consider insulin Repeat CGM in 6 months
Indeterminate glucose homeostasis	4.5-10% of time >7.8 mmol/l or hypoglycaemia	Close monitoring Dietary modification for hypoglycaemia Repeat CGM in 12 months
Normal	No peaks >11.1 mmol/l and <4.5% of time >7.8 mmol/l	Nil Repeat CGM when indicated

Insulin treatment should be started for those in the CFRD group (based on CGMS criteria) and considered for those in the “impaired glucose tolerance” category if weight gain or lung function is poor.

CGMS results can be affected by a variety of circumstances and will be lower than normal if the subject does not eat during the profile or higher if they are unwell or on steroids.

OGTT
Two-hour post glucose challenge value ≥11.1 mmol/L (or fasting glucose ≥7.0 mmol/L) confirms diabetes and treatment should be started. In CF, individuals who do not reach the

diagnostic criteria for diabetes based on OGTT can still benefit from treatment. Insulin has been shown to benefit individuals who fall into the "impaired glucose tolerance" category as well as those with diabetes. If CGMS is not possible treatment should be considered for individuals with impaired glucose tolerance if they have poor clinical status.

A profile of capillary glucose tests should be performed after an abnormal OGTT to guide treatment.

Random blood glucoses
Multiple blood random glucose levels over 11.0 mmol/l will confirm a diagnosis of diabetes, but further tests such as CGMS may be helpful before starting insulin.

HbA1c
The value as a screening test for diabetes in CF is not clear. However, HbA1c is an accurate reflection of average glucose in CF, and if the HbA1c is over 48mmol/mol (6.5%) average glucose levels are over 8 mmol/L and further investigations are needed.

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.**

Management

A weekly CGM review meeting is held on Thursday mornings with Dr Bridges, Dr Alexander, Katie Dick (CFCNS), Caroline Devon (CFCNS) and Delyth Jones (dietitian). Any other Diabetes queries from outpatients or Ward patients can be brought to this meeting.

Who should be treated?

Treat with insulin:
- Everyone who meets the criteria for a diagnosis of diabetes or falls into the CFRD category on CGMS unless there are overwhelming clinical or psychological reasons preventing this.
- Everyone with symptomatic hyperglycaemia.

Consider treatment with insulin:
- Those who have abnormal results (impaired glucose tolerance on CGMS or OGTT) which do not meet the criteria for diabetes but:
    - There is declining lung function or nutritional status with no other cause found.
    - Nutritional concerns, for example on overnight feeds or supplements and not gaining weight.

What insulin to start

Discuss treatment with one of the paediatric diabetes team - these decisions are not made by the respiratory team.

Many individuals with CF can manage on one type of insulin, either once daily Levemir (long acting) or Novorapid (short acting) with meals. It is helpful to look at the CGMS before starting.

- If there are peaks of high glucose through the day start on Levemir before breakfast.
- If there is a single peak around the evening meal, start once daily Novorapid, given just before the evening meal.

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.

Monitoring after starting insulin

- Glucose checks: Glucose should be checked 4-6 times per day for the first few days, varying the times to check before and 2 hours after meals. Everyone on insulin treatment should monitor blood glucoses regularly and they must vary the time they measure. Once a day (varying the time of day) is sufficient for those on once daily insulin but individuals on multiple dose regimens should monitor more frequently (4-6 times a day ideally).

- HbA1c: this accurately reflects glucose levels in CFRD but is a less helpful guide to overall control, than in type 1 diabetes. Measure HbA1c when a child with diabetes is admitted, and when they come to clinic unless it has been checked in the last 2 months.

- Repeat CGMS can be helpful for children on insulin treatment:
  - If control is persistently poor despite adjustment
  - To check that overnight feeds are adequately covered
  - If blood glucose measurements do not fit with the HbA1c level

Adjusting insulin doses after starting

- Ideally only change one thing at a time.
- Go up by 1 to 2 units at a time
- The effect of a change in long acting insulin may take over 48 hrs to be clear.
- For individuals on once daily Levemir, if levels after meals remain high despite increasing Levemir dose, consider adding in Novorapid.
- Remember the time course of the insulin- Novorapid lasts 2-4 hours, Levemir 16-20 hours and Glargine up to 24 hours.

Covering overnight feeds

- Give Levemir to cover overnight feeds, injecting 1 hour before the start of the feed. Adjust the dose, looking at glucose in the middle of the feed and at the end. Mixed insulins or isophane insulin are options if this is not successful.
- If feeds are not given every night, specify a dose for the nights with feed and nights without.

- It is important to get reasonable glucose control while the feed is going in- if the glucose is high during the feed, the calories in the feed will be lost in the urine.

Modulator therapy

Starting modulator therapy (especially Kaftrio) can improve insulin secretions so some individuals need to reduce insulin doses in the months after starting, and occasionally can stop altogether. Discuss monitoring glucose levels and reducing the insulin dose if glucose levels fall or there are hypoglycaemic episodes.

Glucose and insulin management during steroid treatment and infective episodes

Steroid treatment or significant infection can increase glucose levels in individuals on insulin (who will require a dose adjustment) and may result in abnormal glucose levels in those who have normal glucose tolerance at other times. Glucose levels should be monitored if steroid treatment is started, or a patient is admitted for treatment of infection.

Individuals already treated with insulin:

- Should have regular glucose monitoring and ensure measurements cover the whole day
- Insulin doses should be adjusted to cover high glucose levels. Increasing the dose of morning Levemir should be the first step if glucose levels rise as a result of steroid treatment.
- Doses may need to be adjusted down after steroids are stopped or the infection is treated.

Individuals not on insulin- Consider temporary treatment if they have glucose levels over 11.1 mmol/l on several days:

- if the episode is likely to be more than a week
- if improved glucose levels are likely to have a positive clinical impact- persistent high glucose can make infection more difficult to treat
- if there are symptoms of hyperglycaemia
- anyone with elevated glucose during steroids or infection should be reassessed after treatment to check glucose levels have returned to normal
- temporary treatment may be needed only during the inpatient stay

Dietary advice

The family should have input from the dietitians 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 healthy balanced 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 can be substituted with no-sugar-added drinks (*i.e.*, diet/zero fizzy drinks and squash though ideally water is drunk).

Regular eating: Encourage three regular meals and snacks per day. This makes 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 anxiety about the needles.

Hypoglycaemia: Hypoglycaemia is a blood glucose <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. 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 e.g.,100ml of sugary drinks (e.g., Lucozade Energy Coca-Cola, or a carton of juice); 3 glucose tablets; 2 tsp. of jam/honey/syrup; 100 mls of Glucojuice.
- 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 in individuals who are not taking insulin (from endogenous insulin production) are also seen in CFRD and glucose intolerance. Typically, this is after meals and can be improved by avoiding very sugary meals.

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 or Freestyle Libre sensors are added to the regular prescription. Pharmacy at RBH does not keep glucose meters. Most children will need 4 mm needles for their pens.

Outpatient follow up and advice

Royal Brompton Hospital

Nicola Bridges or Saji Alexander comes to the CF clinic on the 3rd Friday and 1st Monday afternoon of each month. If possible, arrange follow up in this clinic.

Some patients will have diabetes follow up arranged in their local hospital. It is important that all 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 to adult services
There is a regular diabetes clinic in adult outpatients at the Royal Brompton with Dr Rebecca Scott. 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. Everyone on insulin should test regularly even if glucose control is very good. Children on lower doses of once daily insulin must test at least once a day, varying the time and those on more complex insulin regimens should test 3-6 times a day 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.

Freestyle Libre Flash Glucose Monitoring system has been approved by NHSE in people with CFRD on insulin treatment. This may be a useful monitoring tool in children who are on multiple doses of insulin but less so in children on a single dose of basal insulin, but they must be prepared to wear the sensor regularly and scan enough to get sufficient information. Patients should be discussed on an individual basis. See RBH Trust guideline ‘Guidelines for the Use of Flash Glucose Monitoring (Flash Libre) for Adult and Paediatric Cystic Fibrosis Patients with Diabetes’.

If a child with diabetes is admitted to the ward

Please call Nicola Bridges or Saji Alexander to discuss the patient, even if things appear to be going well. This can usually be done remotely, or queries brought to the Thursday review meeting. Please call or email for advice on diabetes management, ideally contact at the start of admission to allow time to review and make adjustments.

- 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

- All staff who deal with insulin treatment should have appropriate training.
- 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 and clinic letters 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. However, we use electronic prescribing only.

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 injection technique.
- Always use an insulin syringe to draw up insulin for an intravenous insulin infusion.

Surgery

Many individuals with CF related diabetes can maintain normal glucose levels during fasting without insulin. For children on low doses of insulin this can usually be omitted on the day of surgery. Monitor glucose levels every hour as with other types of diabetes.

If on higher doses of insulin, 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.

Liaise with the C&W diabetes team in advance to make a plan.

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: https://www.bsped.org.uk/

Other practical aspects

Schools.

Diabetes management should be added to the healthcare plan for school. Times for glucose testing and insulin should be clarified, schools may have experience managing children with type 1 diabetes and should be made aware of the differences.

School staff should have training if needed, they have a responsibility to supervise or give insulin and measure glucose levels during the school day if this is needed (so staff can support lunchtime insulin or testing glucoses at school if needed). The JDRF website has relevant information for schools about type 1 diabetes, and much of this applies to CFRD.

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 (see appendix 15). 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. Please check DVLA for the most up to date information.

Useful links

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, their 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 deficiency in childhood related to CF. Centile position at birth is similar to the unaffected population but falls during childhood and at 19 years median centile position is 27% (CF Registry UK report 2017). 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/ inflammation, nutritional factors, abnormal glucose levels 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 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 interval between measurements should be 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 (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 7.6).
- 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 left 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 several studies of the use of GH in CF patients (without GH deficiency) which have demonstrated short-term anabolic, pulmonary function and bone health benefits. However, 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 licensed for use in CF without GH deficiency. There is also a recognised concern that GH may worsen CFRD.

Weak androgens like Oxandrolone have been shown to improve short-term prepubertal growth velocity in children but are not routinely used because of supply issues.

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.

Mean age of menarche is delayed in CF by up to 1.5 years (14.5 years compared to 12.9 years). Menstrual irregularities may also be relatively more common in CF adolescents.

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 increases during puberty and peaks in the years after the end of puberty, because 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. Used in these doses, treatment does not have an adverse effect on adult height.

Steroid treatment for induction of puberty

Oral and topical sex steroids can be used but treatment options are currently reduced due to a shortage of oral ethinyloestradiol. There is a guideline for treatment agents and doses in males and females on the website of the British society of paediatric endocrinology (BSPED) https://www.bsped.org.uk/.

8.4 Bone Metabolism

Bone density in CF

Approximately 20-35% 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. In general, bone mineral content and density are normal in children with a good nutritional status and preserved lung function.

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

The pathophysiology of CF bone disease is multifaceted with effects on bone modelling , resorption and turnover , with the following being the main risk factors contributing to poor bone mineralisation.

- S**teroids** 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 dairy products and consider supplements in those who do not. **A negative calcium balance adversely affects bone health.**

- **Nutritional status-** nutrition apart from calcium and vitamins influences bone growth. CFRD and a low BMI 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 is in DEKAs Plus multivitamin, which is prescribed to all CF children, regardless of pancreatic status.

- **Respiratory infection and systemic inflammation-** 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.

- **CFRD** may be a potential risk factor for reduced bone density.

Screening of bone density

Annual screening bloods should include bone profile and Vitamin D.

Bone densitometry (DEXA scans of lumbar spine and femur) is measured in all patients at the time of their **annual review aged 10 and 15 years**. Look at the vertebrae on chest x-rays for any evidence of injury/crush fractures. This strategy is based on European guidelines and local consensus.

Repeat the scan earlier if:
- **BMD z score is -1 to -2, repeat every 2 years**
- **BMD z score is less than -2.0 or low trauma fracture - repeat in 1 year**
- 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.
- Encouragement of weight bearing exercises.
- Tobacco use adversely affects bone density. So does excessive alcohol and caffeine consumption.

- Least effective dose of steroids.

Management of reduced bone density and osteoporosis

Consider the following factors if BMD z score is < -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.

Measure PTH.

Non-pharmacological treatment :

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. – Vitamin D supplementation ensuring a calcium rich diet with PERT to avoid faecal loss.

Pharmacological treatment (Bisphosphonate treatment)

Bisphosphonates are antiresorptive agents that inhibit bone resorption by inducing osteoclast apoptosis and result in increased bone density. There have been several studies including a metanalysis of bisphosphonate use in adults and young people with CF demonstrating increased bone density with treatment. Bisphosphonates have been demonstrated to reduce fracture risk in a range of other clinical situations, but data on fracture reduction in CF is lacking.

Choice of agent: Zoledronic acid, given once or twice a year as an intravenous infusion would be our choice of bisphosphonate in all ages. See Guy's Paediatric Formulary for doses. There are several oral formulations, but they have poor bioavailability and there are significant cautions about how the tablets should be taken which may limit use in children.

Bisphosphonates have significant side effects and therefore, there needs to be careful decision making about use of bisphosphonates.

In children and adolescents, bisphosphonate treatment should be considered if:

Contributory issues have been addressed AND
BMD z score </= -2 OR vertebral compression fracture AND

- History of low trauma extremity fractures or
- Awaiting or undergone a lung transplant or
- Glucocorticoid use >3months or
- Frank bone loss on repeat BMD

Potential side effects of bisphosphonates:

- Osteonecrosis of the jaw can occur and those with poor dental hygiene are at most risk. A dental check is mandatory prior to start of bisphosphonates.

- There is an increased risk of atypical fractures of femur in adults

- Acute phase reaction and flu like symptoms - studies using IV bisphosphonates suggest these may be more severe in CF.

- Hypocalcaemia- Calcium and Vitamin D status should be replete.

- Bisphosphonates are teratogenic in animal studies and are contraindicated in pregnancy. Because they bind to bone and are then leached out over a long period there is a theoretical risk that a fetus could be exposed if the mother had treatment in the years before pregnancy. Outcomes of a very small number of pregnancies where the mother has taken bisphosphonates have not demonstrated serious adverse effects.

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

The Cf Trust has a document – Cystic fibrosis and bone health.
https://www.cysticfibrosis.org.uk/sites/default/files/2021-01/Cystic%20fibrosis%20and%20bone%20health%20factsheet%20January%202021.pdf

8.5 ENT complications

8.5a Nasal polyps

- Are rarely seen in children other than in cystic fibrosis and may occur in up to 45% of adults and children with CF. In children, about half of these will be asymptomatic.
- Aetiology is unclear but is associated with chronic inflammation and may be related to infection, allergy, immune factors, altered secretions and abnormal cilia.
- 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 examining the nasal cavities with a light but sometimes it is difficult to differentiate polyps from inflamed turbinates.

If troublesome:

- Initial treatment is usually with a nasal steroid spray such as fluticasone (Flixonase or Avamys) or mometasone (Nasonex); see BNFc for dosages. Use of drops in the form of betamethasone or fluticasone (Flixonase Nasules) for periods of up to several weeks at a time often reduces nasal polyposis significantly. Note though that adrenal suppression and growth failure has been reported with protracted use of betamethasone nose drops.
- Saline nasal douching is usually helpful, with Sterimar or NeilMed sinus rinse (see below), which should be used before topical steroid administration.
- Anti-histamines are of no value unless co-existing allergy.
- If persistent severe obstructive symptoms or headache, surgery should be considered, but due to the high recurrence rate (60-90%), multiple procedures may be necessary. Surgery may also be considered if chronic rhinosinusitis with polyposis felt to be a source of respiratory tract reinfection with Pseudomonas.
- Oral steroid courses are occasionally used for severe multiple recurrent polyps.

If conservative therapy is failing, refer to Mr Daniel Tweedie, consultant at Evelina London Children's Hospital who does a monthly clinic. Although highly unusual, if there is an acute complication with an in-patient, refer to the on call ENT team at Evelina.

8.5b Sinusitis

- Although almost all children with CF have chronic paranasal sinus retention of secretions and mucosal inflammation, many are asymptomatic.
- 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 or nasal lavage samples (see below) 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, usually in the form of a macrolide, or based on sensitivity studies, may be of value (3-6 weeks), and oral metronidazole may improve halitosis.
- Teach nose blowing to children unable to do so.
- Mucoactive nebulised medications (dornase alfa, hypertonic saline) may be given via a nebuliser face mask rather than mouthpiece to help direct therapy to the upper airways

and help with obstruction. Intermittent nasal inhalations are recommended.
- Dornase alfa can also be given nasally via a Pari sinus nebuliser to help with upper airways obstruction (see below).
- If *Pseudomonas aeruginosa* is isolated from the nasal swab or sinus rinse sample, then nebulised antibiotics such as Colistin or Tobramycin may be given nasally via a Pari sinus neb (see below).
- 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 saline nasal douche/nasal rinse may give symptomatic relief (see below).
- In a minority endoscopic sinus surgery is appropriate if persistent sinus distribution localised headaches, usually combined with persistent offensive nasal discharge persists despite initial medical treatment with antibiotics and steroids. Persistent Pseudomonal infection may warrant surgical intervention.
- 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 hypertelorism. Surgery is highly effective in draining the chronic infection and preventing further expansion of the paranasal sinuses.

See appendix 11 for protocol of sinus rinsing.

8.5c Hearing, tinnitus & vestibular dysfunction

There is no known connection between deafness and the basic CFTR mutation. However, hearing loss and tinnitus are reported in people with CF usually secondary to aminoglycoside use. The hearing loss can be attributable to high levels of aminoglycoside or the accumulative use of aminoglycosides over time. This appears to be more common with the use of IV amikacin which is one of the principle drugs used for *M abscessus* complex treatment; we have not used IV gentamicin for many years as it was particularly associated with hearing loss. Some reports of tinnitus do happen with nebulised aminoglycosides, but it is usually attributable to intravenous aminoglycoside use hence the recommendation to regularly monitor blood trough levels for aminoglycosides.

Vestibular dysfunction can also occur leading to disturbed vision when the head moves, dizziness, motion sickness and unsteadiness. You need to ask about it as often not volunteered. It can occur despite normal hearing.

m.1555A>G. There is a mitochondrial mutation m.1555A>G, which predisposes to aminoglycoside ototoxicity. It is rare (1 in 520 estimated), although has a higher prevalence in those with sensorineural deafness. Penetrance was previously believed to be 100% but there has been a report of a child who had normal hearing despite having had IV aminoglycosides previously.

Via the NHSE Southeast Genomic Alliance, we intend to test this on newborn screened infants at their 1st annual review (it is extremely unlikely they will need IV aminoglycoside before then). Over the next 1-2 years we will endeavour to catch up the whole clinic cohort.

If positive, we will check the child's hearing, and we will try and avoid the use of nebulised and IV aminoglycosides. However, this is a very important group of antibiotics for treating *Pseudomonas,* so it may still have to be used in certain cases.

Audiometry should be performed:

- as a baseline at the start of commencing treatment for NTM and repeated after1 year.
- in all children starting on regular 3 monthly IV antibiotics and will be repeated yearly.
- if a child ever has a high aminoglycoside trough level.
- if there is a family history of deafness in a close relative.

Audiology should be arranged by referral to the child's local audiology clinic or if an in-patient at RBH, can be done at Charing Cross Hospital.

If any hearing deficit is detected or tinnitus is reported then consideration of stopping aminoglycoside therapy and switching to alternative treatments should be made.

A systematic review has shown that the antioxidant **N-acetylcysteine** (NAC) has a protective effect against aminoglycoside-induced hearing loss, reducing the risk of ototoxicity by 80% (Kranzer et al, Thorax 2015). We use oral N-acetylcysteine for all IV aminoglycoside courses in every child with CF. We find it has been well tolerated by the children. There are no data on its use for *nebulised* amikacin and we are not using this currently. See formulary for doses.

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.

Finally, it must be remembered that **ciprofloxacin** & **moxifloxacin** 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. Ciprofloxacin can

also cause tendinitis and tendon rupture; this can arise within hours of starting treatment or up to 6 months after stopping. Having said that, we have never had a case in our clinic.

If there is doubt over diagnosis or management, refer to Dr Clarissa Pilkington and her team (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 a presenting feature of CF as well as a complication in those with known disease. It is accompanied by chronic salt depletion and sometimes faltering growth without severe dehydration. It can also present acutely often as part of heat stroke so is commoner in hot weather when there has been inadequate salt and fluid replacement with dehydration. Principal findings are *hypokalaemic hypochloraemic metabolic alkalosis, sometimes with hyponatraemia*. This may be preceded by anorexia, nausea, vomiting, fever and weight loss, in the acute setting this can be mistaken for infective gastroenteritis. Judging degree of dehydration in an acute presentation can be hard, the classic clinical signs of dehydration (sunken eyes, loss of skin turgor) are not always apparent and a comparison of acute presentation weight with last clinic weight is helpful.
Check venous sample in blood gas machine for bicarbonate (which will give other electrolytes also), or venous blood for Cl, Na and K. Acutely oral rehydration solution (Dioralyte or equivalent) or sometimes IV fluids (normal saline +/- potassium chloride) is required. In the more chronic, indolent presentation treatment is with sodium +/- potassium chloride supplements, which may be required for many months or long term. After salt replacement, the metabolic abnormality resolves, and weight gain follows rapidly.
Unexplained faltering growth 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 total body potassium depletion.

It is quite usual for a newborn screened infant under 3 months to have low urine Na levels and normal range is less well defined, so it should **not** be used to guide sodium supplementation in this age group (see salt supplement recommendations in section 7.3).

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! We are uncertain also whether being on Kaftrio will restore fertility in a few males (anecdotal adult experience). 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). It is important to reassure families that men with CF can father a baby.

Girls are not infertile so again contraception must be encouraged. Indeed, there has been a significant increase in pregnancies amongst women with CF who are on Kaftrio and other CFTR modulators. Useful information on types of contraception is available in a booklet entitled 'Cystic fibrosis and relationships' available via CF Trust website (see appendix 19). 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 affect 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.

8.9 Stress incontinence

Urinary incontinence is a condition where certain activities *e.g.*, coughing, laughing, jumping, exercising can lead to a leak of urine. This can range from a few drops to 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 and males (younger and older) may also be affected. There is insufficient evidence to provide prevalence, but one study found that up to 1 in 3 females and 1 in 6 males can have a problem at some time. Often children may not tell their parents or the medical team about this as it can feel embarrassing, or they may not think it is important. Sometimes girls may find it easier to speak to a female member of the team about this.

If urinary incontinence is identified as a problem: initially they can be seen by one of the physiotherapy team and taught some simple 'pelvic floor exercises' and a technique known as 'the knack' (a pelvic floor contraction) which can be quite helpful. Some bladder and posture management may also be recommended. Should further input be required we can refer on to a gynaecologist and/or pelvic heath physiotherapist. Ensure there is no vaginal candidiasis as there is an increased risk in the presence of incontinence.

Older children may find the NHS Squeezy App useful www.squeezyapp.co.uk. Useful patient information leaflets are available at the CF Trust.

Please note that for some patients (males and females) faecal incontinence may be an issue.

9. Lung 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, Paul Aurora or Rossa Brugha. A referral proform is available from Great Ormond Street Hospital – heartlungtransplant@gosh.nhs.uk. 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 Drs Martin Carby, Anna Reed or Vicky Gerovasili, Consultants in Respiratory & Transplant Medicine, at Harefield Hospital.

In the past, 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. Now though, bilateral lung transplant is the operation of choice. 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 performed in paediatric practice in the UK.

Consideration of a child for LT 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.

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).
- Infection with *Burkholderia cenocepacia* and *Mycobacterium abscessus* - all subspecies.

- Child does not want the procedure despite receiving and understanding 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.,* non-abscessus NTM, some genomovars of *B cepacia* complex, *MRSA*, pan-resistant *P aeruginosa*, treatment-resistant fungi.
- Severe osteoporosis.
- Some extreme psycho-social issues, for example, long standing and entrenched nonadherence to treatments despite interventions.

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 20% of patients will die before organs become available. The time spent waiting for organs may be stressful (uncertainty, false alarms etc).

2. Lung transplantation is not a complete cure for CF, it is a palliative procedure with a median survival of 10 years. After the operation, invasive procedures including bronchoscopy and biopsies are 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 nebulised antibiotic therapy and physiotherapy necessary.

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

4. Problems associated with transplantation include early rejection, infection related to immunosuppression and later development of Chronic Lung Allograft Dysfunction which can eventually lead to severe respiratory impairment and is difficult to treat successfully.

10. Miscellaneous

10.1 Preparation for surgery

It is important to ensure that BOTH the parents and child/young person have a clear understanding of what the surgery is for, and what the outcome of surgery will be. Consent will be obtained by the surgeon.

Pre-op nil by mouth -
6 hrs food and bottle milk
4 hrs breast milk
2 hrs water

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, dental procedures, ENT surgery such as polypectomy, tonsillectomy and gastrointestinal endoscopy. We do not do this for bronchoscopy, however. 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 severe lung disease (FEV_1<40%, or oxygen-dependent) can be at high risk from anaesthesia and surgery, so the risk benefit of the procedure must be carefully considered, and pre-op assessment by the anaesthetist should be carried out. Their health status must be optimised prior to the operation.
- **Pre-op plan** for those with significant lung disease – IV antibiotic course (pre and post), IV fluids when NBM, see Pain Team for planning, organise postop on call physiotherapy, consider NIPPV post op, early mobilisation.
- 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 is often done at start of 14 day IVAB course when patient not doing well and no microbiology available or nothing ever grown.

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. We also recommend the whole family are vaccinated. The vaccines are usually available in October each year.
We follow the NHS policy –

Under 6 months	No vaccine	
6m – 2yrs	Inactivated injected vaccine	• Deep subcutaneous or intramuscular injection. • If never had before (and <9yrs old), they get 2 doses 4 weeks apart.
2 yrs and above	Live attenuated nasal spray vaccine.	• If never had before (and <9yrs old), they get 2 doses 4 weeks apart. • Not to be given if large bilateral nasal polyps. • Contraindicated if severely asthmatic.

Egg hypersensitivity with evidence of **previous anaphylaxis** is a contraindication, although NHS guidance suggests children with milder egg allergy can receive the nasal vaccine. Parents should also receive the vaccine (but we do not routinely give to siblings).

Further information is available on:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/456568/2904394_Green_Book_Chapter_19_v10_0.pdf

COVID-19 vaccine – we suggest following the national guidance, which offers it to all people aged 5 years and above, since April 2022.

Pneumococcal vaccine - Prevenar is given as part of national immunisation policy, and Prevenar 13 covering 13 serotypes was introduced in April 2010. In older children who did not receive Prevenar, if the parents are keen, we would have no objection to them having the vaccination, although it is not routinely recommended, as Pneumococcus is not an organism particularly associated with CF. Pneumovax (a pneumococcal polysaccharide 23 valent vaccine) 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, Colindale (tel. 0208 327 7471).

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 (IgG), 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. We are undertaking a period of catch up with this protocol. Varicella antibody results should be checked when starting someone on oral steroids for ABPA.

10.4 Travel abroad

Patients will need:

1. An information fact sheet which is available from the CF Trust (020 3795 1555).

2. Advice is also available in the BTS clinical statement on air travel (updated 2022).

3. Adequate travel insurance. They need to be advised to fill in the medical information in 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. A GHIC card should be obtained, they have replaced EHIC cards and may help with healthcare costs in EU countries.

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. Pulmozyme 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.

8. Letter for customs explaining the need for all the drugs and equipment – available in clinic or from the CF secretary (appendix 15). There is a separate letter available for those with CF related diabetes.

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 currently at Evelina but in future will again be available at RBH. 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. 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 Palliative care

Death in childhood is a very unusual event amongst our CF population. If the possibility of death becomes more likely an early referral to the palliative care team is beneficial. The team can offer support with symptom management, advanced care planning and liaison with local and community teams.

The principles of good palliative care are ensuring the child's comfort is prioritised and the child and families' wishes are explored. This may affect their choice of place of care and escalation of treatment. A child/family may choose to receive their care in the Royal Brompton, hospice or home. A clear discussion will be had with the child and family to ensure that they are clear about the level of provision (both medical and nursing support) available in each setting.

If the child/family choose to stay in hospital the CF team will lead on their day to day care with specialist advice from the palliative care team. This can be provided both face to face and via telephone/video. These children will need at least daily medical review to ensure their symptoms are well managed.

If the child/family choose to stay at home or transfer to a hospice, the palliative care team will lead on their care in close liaison with the CF team and utilising local paediatrics teams, hospice and children's community nursing teams.

Good communication between teams is essential to ensure that the family are receiving consistent messages from all involved. Regular multi-disciplinary-team meetings are helpful along with group emails to teams involved.

End of life care will be discussed with the parents by the child's consultant and the palliative care team. 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 end of life care and is not disadvantaged by false hopes of a last-minute donor organ becoming available.

Specialist Paediatric Palliative care services are available to provide symptom management, support advance care planning and end of life care. An early referral to the team allows time for relationship building and time for families to reflect on their priorities.

The Evelina Paediatric Palliative Care Team can be contacted– during office hours available on 07747267799 or out of hours via the GSTT switchboard on 0207 1887188 or non-urgent contact via email on paediatricpalliativecare@gstt.nhs.uk.

This team look after infants, children and young people up to the age of 18yrs. There is a two- tiered 24/7 telephone on call service for professionals and families with a consultant backup.

A referral form needs to be completed (available on request) with a phone call to discuss the urgency of need.

End of life care – the process

Please also refer to the Royal Brompton Hospital policy document - "Guidelines for the management of patients and families during death and bereavement" available on the Trust Intranet, and NICE guidance for End of life care in children and young people.

- If the family wish, the palliative care team may complete an Advanced Care Plan with the family/child documenting their preferences for place of care, escalation of treatment and processes around death (including organ donation).

- The palliative care team will provide a symptom management plan to be used in hospital or home/hospice as the child/family wishes, in conjunction with the ACP.

- Clear and open discussions about the appropriateness and need for specific observations, interventions and treatments should be discussed with the family (and child where appropriate) 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 CF nurses should continue and local services and involved professionals should be updated on any changes in the child's condition.

- The palliative care team will look to rationalise medications ensuring that only those providing symptomatic relief are continued

- 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.

- Psychosocial support by the psychosocial team including the CF clinical nurse specialists, family liaison team, psychology, play specialists and chaplaincy team) is offered to the patient with CF and their family. This is closely planned and offered to the family to prevent them feeling overwhelmed with support at such a difficult time.

- Each child and their family have specific cultural and religious needs, these should be sensitively explored. There is a hospital chaplain (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 family's local faith leader is welcomed if preferred by the family.

- Support for RBH staff both formal and informal is offered and all team members are encouraged to participate in treatment (or non-treatment) planning at all times.

The Advance Care Plan includes a **Do-not-resuscitate** (DNRCPR) for use in the community but should the child/family choose to remain in hospital local paperwork should also be completed. Discussions around this should be had with the family and child (where appropriate) and clearly documented in the medical notes.

Please refer to the Royal Brompton Hospital 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.

Advance care plans and ReSPECT documents are replacing DNRCPR 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. The ReSPECT document is used to traverse all care and service settings.

Care at home

Should the family have decided to care for their child at home the Evelina London paediatric palliative care team will take the lead role in the child's care, with support from community, hospice and local hospital teams, 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 via the APPM website and is regularly updated. The formulary is written from best evidence and expert advice - https://www.appm.org.uk/.

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

We no longer have medications listed here. Please contact the Evelina palliative care team if the child requires symptom management advice.

Once the child has died

More information is available on the Bereavement portal on the hospital's intranet

- 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 family should be offered the opportunity to take important and valuable memories of their child *e.g.*, handprints or casts, fingerprints (silver casts), if they wish. There should be a memory box with equipment for the ward staff to use. Hospices are an excellent resource and guidance in this area. They have outreach hospice at home nurses who can support staff in this memory making.

<u>Deaths in hospital</u>

- 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 already present.

- Inform the Bereavement team (ext. 82268) indicating that a child has died, giving their name, time of death and patient hospital number and ward.

- A bereavement pack must be given to the family (available on all wards and PALS office). They should also be given the Hospital Trust leaflet entitled 'When Your Child Dies'.

- The doctor will then need to write a medical certificate confirming the cause of death (MCCD). This should be done in conjunction with the child's medical examiner. The book is available on the PICU and Sydney Street reception, or in the PALS office. It is advisable for the doctor completing the MCCD to ensure they have seen the patient after death; this is because it is a compulsory requirement for completing a cremation form. If the death is 'Unexpected' (this is most unlikely with an expected death of a CF patient) then discuss with the on-call consultant.

- 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 or cooled bed for up to 5 days. Parents can visit freely or even stay in the hospice with their child. If going home, particularly during hot weather, it may be necessary for the family to use an air cooling units or mattress. A local funeral director will discuss this with the family, or the team can contact the local hospice who may be able to provide this equipment. This cannot happen until the MCCD has been completed and handed to 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 at RBH and the local hospital 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 normal working hours, either the paediatric family liaison team and/or the RBH Bereavement Officer (ext. 82268, or bleep 7701) will help provide information (including written literature) for the family. The CF CNS and/or family liaison team will be the main contact with the family once the child's body is no longer on the inpatient unit.

- 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 Registrar at the Town Hall.

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

Deaths at home or hospice

- The family will contact the palliative care when they feel able, team who will advise on next steps.
- The child's death will need to be confirmed by the community/hospice nurse, GP or paramedic.
- The Medical Certificate of Cause of Death (MCCD) may be completed by the child's GP or hospice GP.
- The family may prefer to keep the child at home for a short time or transfer the child to the local hospice bereavement suite. The palliative care team can support the family with this process.
- The palliative care team will inform the professionals involved if the death occurs at home. If the death occurs in the hospice the team there will inform professionals involved.

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 and the MCCD has been completed by a doctor who has cared for the patient. 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 of Cause of Death (MCCD)'. 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 hospital MCCD 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.

If the family wish to move the child, please contact the palliative care team to support this. We would recommend utilising a funeral director for transfer home or to the hospice. We would not recommend the family drive themselves due to emotional upset and risk of accident but instead enlist help from friends/family members.

If the family chose not to utilise a funeral director, then they will need:

1. The MCCD.
2. A letter (written by a doctor or nurse) stating
    a. Date
    b. Child's name, date of birth and that the child has died
    c. Address they are travelling from
    d. Address they are travelling to

e. Contact details of the doctor or nurse in the case the family are stopped on route by police.

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)

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 to try to access support in the community. There are various online and telephone support forums/sites including:
  -Child death helpline (0800 282 986 | 0808 800 6019)- run by bereaved parents for bereaved parents
  - www.childbereavementuk.org
  - www.togetherforshortlives.org.uk/families/familys_journey/bereavement_support
  - www.cruse.org.uk
- The CF team should signpost the family to local bereavement services. This can be supported by the specialist palliative care team or the local hospice.
- Another invitation given routinely is to the hospital commemorative ceremony for children who have died. This is an annual event (late Oct/early Nov), comprised of words and music, open to those of any or no religion. Although the hospital chaplaincy and other religious leaders attend, 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.
- The palliative care team will contact families by phone or text following the death of their child. They will signpost families to financial assistance available.
- Staff 'debrief' meetings, facilitated by representatives from the paediatric clinical psychology team, are offered to all involved. Additional support is offered to staff as requested.

3. Child death review process

It is a statutory requirement to notify the Child death overview panel (CDOP) of all child deaths from birth up to their 18th birthday. After the child dies a child death notification form should be completed by the team looking after the child when they died. A Child death reporting form may be completed by other professionals involved in the child's care. The purpose of this form is to gather a wide range of information about a child's death and his/her illness. Its primary purpose is to enable CDOP to review all children's deaths in their area in order to understand patterns and factors contributing to children's deaths. This information contributes to the national child mortality database. A child death analysis form should be completed after a child death analysis meeting (similar to mortality meeting) which reviews the child's care and death and also reviews any questions raised by parents/carers. This should be completed within 3 months of the child's death.
(https://www.gov.uk/government/publications/child-death-reviews-forms-for-reporting-child-deaths)

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 - <u>PROPHYLACTIC DOSES</u>

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 only if regularly grows *H influenzae*. May discolour teeth. We do not use for Staph prophylaxis. Caution with CF liver disease **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	125mg bd (This dose is for prophylaxis in those < 3 years, and those in CF START study) Older children: 50 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*.** Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Caution in CF liver disease.

11.1b ORAL ANTIBIOTICS – <u>TREATMENT DOSES</u>

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 Once able to swallow tablets: 25-40 kg: 250mg od >40kg: 500mg od Usually 10 days.	For *S aureus, H influenzae* and *mycoplasma* Ten days gives about 1 month's coverage. *Potential* for hepato- and ototoxicity but usually *very* well tolerated. Can cause tooth and tongue discolouration. Can prolong QT interval
Chloram-phenicol	Oral	>1 month: 12.5 mg/kg qds. Occasionally use 25 mg/kg qds (Max 4 gms/day). 2-3 weeks course	Consider for *S maltophilia, P aeruginosa, B cepacia, S aureus*. Needs full blood count at day 21 if course longer than 3 weeks. Parent/carer should be advised to contact their doctor if they experience sore throats, fever, mouth ulcers, unusual or increased bleeding or bruising. Preferably round dose to the nearest whole capsule (250mg). Capsules can be opened, and the contents mixed with water or orange juice and given immediately. Levels should be considered in all patients receiving higher doses of 25mg/kg qds, children < 4 years old and patients with hepatic or renal impairment. Aim trough level of <10 mg/L and 2 hour post dose level 10-25 mg/L after at least 1 day of therapy.

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. **3 weeks for 1st isolation.** ***Consultant decision*** to exceed this length. Usually 2 weeks for exacerbations.	**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. Milk **will** reduce absorption. Avoid milk for at least 30 mins before and after taking ciprofloxacin. Also used for NTM treatment – ***consultant decision.*** See section 6.2a 6 VII. Can prolong QT interval. Joint pains occasionally – risk of tendonitis and tendon rupture – consider withdrawing treatment Parent/carer should be advised to stop ciprofloxacin and contact their doctor if they experience: - Tendon pain, swelling or rupture (can arise within 1 hour of starting treatment or up to 6 months after stopping) - Pain in joints or swelling in shoulder, arms or legs - Abnormal pain or sensations (*i.e.*, tingling) esp. in legs or arms - Severe tiredness, depressed mood, anxiety, or problems with memory or severe problems sleeping - Change to vision, taste, smell or hearing
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) 2-4 weeks	Cheaper alternative to azithromycin. Can cause tooth, tongue & urine discolouration. Part of NTM protocol. Care needed as interacts with some drugs *e.g.*, itraconazole, rifabutin, ivacaftor, Orkambi, Symkevi and Kaftrio – check BNFc & discuss with paediatric pharmacy team. Can prolong QT interval

Clofazimine	Oral	<30kg: 50mg od 30kg and above: 100mg od Max dose 100mg od US/ECFS recommend 1-2 mg/kg BTS 3-5 mg/kg Our dose is a compromise	*Consultant decision* – reserved for the treatment of NTM. Take with or just after food. May cause a discoloration of the skin from red to brownish-black, as well as red staining of sweat, sputum urine, faeces, tears, and saliva. Patient/carer should be advised that skin discoloration, although reversible, may take several months or years to disappear after the stopping therapy. Photosensitising so warn patient re sunlight. High strength sunblock should be used in summer or on holidays for 4 weeks after course finished. Advise patient/carer to seek medical advice if persistent abdominal symptoms develop (pain, diarrhoea, nausea, vomiting). Can prolong QT interval. Do ECG prior to start of therapy and 2 weeks after, then if adding other drugs that can cause QT prolongation.
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 1 month	For *S aureus* and *H influenzae* Caution in CF liver disease
Co-amoxiclav **250/62**	Oral Susp	1-<6 yrs: 5ml tds 6-12 yrs: 10ml tds 1 month	
Co-amoxiclav **500/125**	Oral tablets	>6 yrs: (625mg tabs) 1 tab TDS 1 month	Co-amoxiclav 625mg tabs are to be used in preference to 2 x 375mg tabs to reduce clavulanic acid intake.

Co-trimoxazole	Oral	6 weeks–5 months: 120 mg bd 6 months–5 years: 240 mg bd 6–11 years: 480 mg bd 12 years +: 960 mg bd 1 month	Use mainly for *S maltophilia* & MRSA. Maintain adequate fluid intake Monitor FBC 4 monthly if on prolonged treatment e.g., for NTM. 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.
Doxycycline	Oral	8-11years: 4.4mg/kg (max 200mg) od ≥12 years: 200 mg od 2-4 weeks (can be used long term)	Can be useful for *S maltophilia* and *B cepacia*, and MRSA ***Consultant decision*.** Patient should preferably be ≥12 years (due to discoloration of growing teeth and bone). However, can be used in 8-11 year olds in severe infection with no adequate alternatives, once confirmed with dental professional all 'adult' teeth in place. Take standing or sitting upright with 200 ml water (to avoid oesophageal irritation). Photosensitivity (see ciprofloxacin). Caution in CF liver disease. Benign intracranial hypertension - if visual disturbance and headaches occur during treatment, prompt ophthalmologic evaluation should be carried out.
Ethambutol	Oral	15-20mg/kg od	***Consultant decision*** – reserved for the treatment of NTM. Monitoring - Visual acuity & colour vision testing at baseline and if symptoms reported, advise patients to report visual changes if possible. However, in very young children unable to report symptoms suggest routine ophthalmological examinations every 6 months. Peripheral neuropathy.

Flucloxacillin	Oral	30-35 mg/kg TDS MAX 4 gms/day 1 month	Give 1 hour BEFORE meals or on an empty stomach. Liquid tastes awful – different brands may be tolerated better than others. If using capsules round dose to nearest capsule size i.e., 250mg or 500mg. Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Caution in CF liver disease.
Fusidic acid	Oral	Using liquid: <1 yr: 15mg/kg tds 1-4 yrs: 250 mg tds 5-12 yrs: 500 mg tds > 12 yrs: 750 mg tds Using tablets: > 12 yrs: 500mg sodium fusidate tablets tds 2 weeks	Caution in CF liver disease. Liquid should be taken 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.
Linezolid	Oral	<12 yrs: 10mg/kg (max 600mg) **tds.** ≥12 yrs: 600 mg bd 10 day course	2nd line for *MRSA* or *S aureus* where patients have not responded to conventional agents *e.g.*, high dose flucloxacillin, rifampicin, fusidic acid. Aim for 10 day course and if course<14 days we do not do routine FBC. Occasionally used for NTM - consider use of pyridoxine (B_6) to reduce risk of cytopenias. ***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. Where possible patients should be warned to immediately report any visual changes, regardless of treatment duration. Monitor FBC weekly for courses of 2 weeks or more.

Minocycline	Oral	8 - 11 years: 2mg/kg (max 100mg) bd ≥12 yrs: 100mg bd 2 weeks	Can be useful for *S maltophilia, B cenocepacia* & resistant *P aeruginosa.* ***Consultant decision*.** Patient should be ≥12 years (due to discoloration of growing teeth and bone). However, can be used in 8-11 year olds in severe infection with no adequate alternatives, once confirmed with dental professional all 'adult' teeth in place. Caution in CF liver disease. Take standing or sitting upright with plenty of water (see doxycycline). If treatment > 6 months, monitor liver function tests every 4 months.
Moxifloxacin	Oral	10mg/kg (max 400mg) od	***Consultant decision*** – reserved for the treatment of NTM. **Not** active against *P. aeruginosa* or MRSA Joint pains occasionally – risk of tendonitis and tendon rupture – consider withdrawing treatment Parent/carer should be advised to stop ciprofloxacin and contact their doctor if they experience: - Tendon pain or swelling - Pain in joints or swelling in shoulder, arms or legs - Abnormal pain or sensations (*i.e.*, tingling) esp. in legs or arms - Severe tiredness, depressed mood, anxiety, or problems with memory or severe problems sleeping - Change to vision, taste, smell or hearing Can prolong QT interval. The manufacturer advises should not be used concurrently with other drugs that prolong the QT interval: risks and benefits must be considered if this is deemed necessary. Do ECG prior to start of therapy and 2 weeks after, then if adding other drugs that can cause QT prolongation. Caution in CF liver disease.

Rifampicin	Oral	*S aureus* treatment: 10 mg/kg (max 600mg) bd. NTM treatment: 10 - 20 mg/kg (max 600mg) **od.** 2 weeks	2nd line for *S aureus* only in child not on CFTR modulators. Usually give with fusidic acid. Occasionally used for NTM. Give 30 – 60 minutes ***before*** food. ***Consultant decision*.** Caution in CF liver disease. Please note rifampicin interacts with many drugs (including ivacaftor, Orkambi®, Symkevi®, Kaftrio®, clarithromycin, itraconazole, voriconazole, posaconazole, chloramphenicol, oral contraceptives) so always check in BNFc and with pharmacist. Co-administration with ivacaftor, Orkambi®, Symkevi®, Kaftrio® not recommended – use alternatives. Can cause red staining of urine, tears and saliva.

11.1c INHALED ANTIBIOTICS

See NHSE Clinical Commissioning Policy for inhaled therapy first published Dec 2014.
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/01/a01-policy-inhld-thrpy-cf.pdf

Note that for inhaled antibiotics (nebulised and dry powder) 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.

Amikacin (from IV solution)	Nebulised	<12 years: 250mg bd (add 2ml 0.9% saline to 1ml of 250mg/ml amikacin). >12 years: 500mg bd (add 1ml 0.9% saline to 2ml of 250mg/ml amikacin). If not tolerated, retry at a lower dose.	Usually for NTM. Can further dilute injection with 0.9% sodium chloride. Suitable for jet nebuliser but not e-flow rapid or I-neb. Avoid using ear bud headphones due to increased risk of hearing problems. For does <500mg use 1 vial per day; keep remaining undiluted solution in the fridge.
Amphotericin (Fungizone®)	Nebulised	<10 years: 5 mg bd >10 years: 10 mg bd The dose can be increased up to 0.5mg/kg (max 25mg) bd depending on clinical response and tolerability	For chronic aspergillus. ***Consultant decision***. No need to use expensive liposomal preparation unless cannot tolerate standard preparation which tastes awful. Only suitable for Jet nebuliser. Can't use e-flow or I-neb. Dilution: 50 mg in 10ml of water for injection. Withdraw required dose and further dilute with water to a minimum volume of 3ml for nebulisation. Use 1 vial per day; keep remaining solution in the fridge
Aztreonam Lysine (Cayston®)	Nebulised	75 mg BD during alternate months We use it **TWICE DAILY**, and only suggest three times a day for particularly troublesome cases. Mix with 1ml 0.17% saline (diluent comes with drug).	3rd line for chronic *P aeruginosa.* Doses should be taken at least 4 hours apart. Pre dose with bronchodilator ***Consultant decision.*** Colistin or tobramycin usually given during the intervening month Should ideally be stored 2-8ºC. but can be

		Not commissioned for continuous use (only for alternate months).	kept out of the fridge, but below 25ºC, for up to 28 days. Used via e-flow but must use special Altera handset which nebulises to dry. Change handset monthly (provided in the box with the drug).
Ceftazidime	Nebulised	1 gm bd Reconstitute 1 gram injection with 3ml water for injection	For *B cepacia*. Tastes awful. ***Consultant decision*** Only suitable for Jet nebuliser. Can't use e-flow rapid or I-neb.
Colomycin (Colistin)	Nebulised	< 2 yrs: 1,000,000 Units bd > 2 yrs: 2,000,000 Units bd Mix with 3ml 0.9% saline. 1,000,000 units = 1 megaunit (Mu) Colomycin - Nebulise in Jet nebuliser or e-flow rapid. **Not** I-neb.	1st line for chronic *P aeruginosa*. Bronchospasm can be reduced by i) pre-dose with bronchodilator. and ii) diluting with salbutamol For Promixin 500,000 unit doses: the reconstituted solution may be kept for up to 24 hours in the fridge, unless reconstituted with salbutamol in which case it must be used immediately.
Promixin (Colistin)	Nebulised via I-Neb	< 2 years: 500,000 units bd >2 years: 1,000,000 units bd Promixin - I-neb only. Use Grey I-neb Chamber.	
Colobreathe turbospin (Colistin)	Inhaled (dry powder inhaler)	1 capsule (1.66 MU) bd via Turbospin powder inhaler	Doses should be inhaled as close as possible to 12 hours apart. Put fat end of capsule into inhaler first to minimise capsule shattering when capsule is pierced.
Meropenem (from IV solution)	Nebulised	6-12 years: 125mg bd >12 years: 250mg bd	Usually for NTM. Also used for *B cepacia* chronic therapy. Reconstitute 500mg vial with 10ml 0.9% sodium chloride - the shelf life once reconstituted varies between manufacturers. Check with pharmacy to determine whether reconstituted solution may be kept for next dose. For a 250mg dose: use 5mls of

			reconstituted solution. For a 125mg dose: use 2.5mls of reconstituted solution and add 0.5mls of 0.9% saline Nebulise in Jet nebuliser not e-flow rapid.
Tobramycin – 300mg/4ml solutions (e.g., Bramitob®) Or 300mg/5ml solutions (e.g., TOBI) Other generic versions are available but not listed here.	Nebulised	300 mg bd during **ALTERNATE MONTHS** Licensed >6 years only	1st line for eradication of *P aeruginosa* given for 1 month. 2nd line for chronic *P aeruginosa.* ***Consultant decision*****.** In chronic *P aeruginosa* colistin will usually be given in the month off tobramycin. In our experience Bramitob® (300mg/4ml preparation) tends to be better tolerated in pre-school children and best given via a jet nebuliser. Use jet nebuliser, E-flow or I-neb. If given via an I-neb will need to be nebulised twice per dose (2 fills per dose) using lilac chamber. After removal from refrigerator, TOBI pouches (intact or opened) may be stored at up to 25ºC for up to 28 days. Bramitob pouches (intact or opened) may be stored at up to 25ºC for up to 3 months. For generic versions please refer to manufacturers' information. When switching between 300mg / 4ml and 300mg / 5ml preparations a DRA is required as solutions have different concentrations. Doses should be nebulised as close as possible to 12 hours apart and not less than 6 hours. Avoid using ear bud headphones due to increased risk of hearing problems.

Tobramycin – Vantobra® 170mg/1.7ml solution	Nebulised	170 mg bd during **ALTERNATE MONTHS** **Note different dose to other tobramycin nebulisers – prescribe as brand 'Vantobra'** May be considered as alternative to Bramitob or tobramycin under physiotherapist guidance.	2nd line for chronic *P aeruginosa*. **Consultant decision.** In chronic *P aeruginosa* colistin will usually be given in the month off tobramycin Used via e-flow but must use special Tolero handset which nebulises to dry. Change handset monthly (provided in the box with the drug) After removal from refrigerator may be stored at up to 25ºC for up to 28 days. Doses should be nebulised as close as possible to 12 hours apart and not less than 6 hours. Avoid using ear bud headphones due to increased risk of hearing problems.
Tobramycin – TOBI Podhaler	Inhaled (dry powder inhaler)	112mg (4 x 28mg capsules) bd via podhaler during **ALTERNATE MONTHS**	Doses should be inhaled as close as possible to 12 hours apart and not less than 6 hours.
Vancomycin	Nebulised	4mg/kg (maximum 250mg) qds for 5 days for eradication Alternatively use BD for 4 weeks *Consultant decision*	MRSA Reconstitute according to manufacturer's instruction (take into account displacement volume). Draw up required dose and make up to a total of 4ml with sodium chloride 0.9%. The shelf life once reconstituted varies between manufacturers. Check with pharmacy to determine whether reconstituted solution may be kept for next dose. Use jet nebuliser. Pre-dose with inhaled or nebulised salbutamol to prevent bronchoconstriction.

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.
ii) Gentamicin is never used due to increased renal toxicity.
iii) Consent MUST be taken, and oral N-acetylcysteine (NAC) prescribed for all patients receiving IV aminoglycosides.
iv) Take care with first doses as unexpected, severe hypersensitivity does occur.
v) 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.
i) We rarely use imipenem - too many side effects and spectrum no different from meropenem.

CIVAS (Centralised Intravenous Additives Service)

CIVAS is outsourced to an external provider.

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.

Amikacin	IV	30 mg/kg od (max 1.5g od)	Aminoglycoside Infuse over 30 mins. Levels at 23 hours after 1st dose (*i.e.*, **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 Only use if resistant to tobramycin or gentamicin. Used for initiation of NTM treatment – *consultant decision* Audiology at baseline. Consent MUST be taken for use of aminoglycosides EVERY TIME GIVEN; and oral N-acetylcysteine (NAC) prescribed for all patients receiving IV aminoglycosides.
Aztreonam	IV	50 mg/kg tds (Max 8 gms per day).	Monobactam No gram-positive activity.

Cefoxitin	IV	50mg/kg tds (Max 12g /day).	Cephalosporin Can give as a slow bolus Reserved for treatment of NTM – ***consultant decision.*** NOT active against *P aeruginosa.*
Ceftazidime	IV	50 mg/kg tds (Max 9 gms /day).	Cephalosporin Unexpected hypersensitivity on first exposure.
Ceftazidime/ Avibactam	IV	6 months - 18 years: 50mg/kg ceftazidime/12.5mg/kg avibactam tds (Max 2000mg ceftazidime/ 500mg avibactam tds)	Cephalosporin + beta-lactamase inhibitor Infuse over 120 minutes. Reserved for resistant *P aeruginosa*, NTM or *B cenocepacia*, as part of a 2nd line treatment regimen, based on in vitro sensitivities. As part of the NHSE Antimicrobial health technology evaluation a Blueteq from should be completed for each patient prescribed ceftazidime/ Avibactam. Please refer to the Paediatric Pharmacy team and notify consultant microbiologist. ***Consultant decision.***
Cefuroxime	IV	Child 1 month and above: 50mg/kg (max 1.5 grams) TDS Can be increased to 60mg/kg (max 1.5grams) QDS if very unwell	Cephalosporin Give slowly over a minimum of 3 minutes
Colistin	IV	25,000 units/kg **tds**	Polymyxin

		(max. 2MU per dose) Higher doses are used for severe sepsis etc, but we do not use that in CF.	Slow infusion over 30 mins. Max concentration is 40,000 units/ml. Boluses (over at least 5 mins) with dose ≤ **2MU** can be used for **Portacaths** only. All doses via PICC lines must be infusions and never boluses. <12 yrs: dilute to 90,000 units/ml. ≥12 yrs: dilute to 200,000 units/ml. Measure renal function once a week. Not a first line agent**. Avoid using with IV amphotericin** (renal toxicity)**.**
Co-trimoxazole	IV	>6 weeks old: 60 mg/kg BD (no upper dose limit)	Useful for *A xylosoxidans & S maltophilia* ***Consultant decision*** Infuse over 60-90 minutes. Maintain adequate fluid intake. Monitor FBC if on prolonged treatment. 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.
Fosfomycin	IV	1-11 months (up to 10kg): 100mg/kg TDS 1-11 yrs (10-39kg): 125mg/kg TDS (Max 400mg/kg daily) 12-17 yrs (>40kg): 8g TDS	Phosphonic acid antibacterial Useful for patients with multi-resistant *Pseudomonas aeruginosa* and/or where allergies are an issue – *consultant decision.* Fosfomycin is associated with a high sodium load - monitor fluid balance during therapy & U&E's twice weekly. Infuse in glucose 5% at a maximum rate of 133mg/minute.
Linezolid	IV	<12 years: 10mg/kg tds (max 600mg tds) ≥12 years: 600mg bd	Oxazolidinone Last line for *MRSA* or *S aureus* where patients have not responded to conventional agents. Infuse over 30 – 120 mins. Monitor FBC weekly. ***Consultant decision*** **Courses >28 days lead 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. Use oral route wherever possible. Otherwise convert to oral route as soon as clinically indicated.
Meropenem	IV	40 mg/kg tds. (Max 2g tds)	Carbapenem Give slowly over 5 minutes. Headache common.
Piperacillin / Tazobactam	IV	>1 month: 90mg/kg qds (Max 4.5g qds)	Ureidopenicillin. Give slowly over 5 minutes. ***Consultant decision*.** Not used unless we are desperate due to rashes and hypersensitivity
Teicoplanin	IV	>2 months – 11 years: 10mg/kg 12 hourly for 3 doses (loading dose) followed 24 hours later by 10mg/kg od. ≥12 years: 6mg/kg 12 hourly for 3 doses (loading dose) followed 24 hours later by 6mg/kg od (no upper dose limit)	Glycopeptide Can give as a slow bolus or infusion over 30 minutes ***Consultant decision*** Therapeutic drug monitoring may be of value in severe infection, MRSA and unexpected therapeutic failure. Discuss need with microbiologist. Aim trough 15 - 60mg/L (taken after at least 7 days). Note levels take 5 days to come back.
Temocillin	IV	25mg/kg bd (Max dose 2g bd)	Penicillin Slow bolus over 3 – 5 minutes ***Consultant decision***. 3rd line
Tigecycline	IV	8 – 11 years: 1.2mg/kg (max 50mg) bd ≥12 years: 50mg bd, reduced to 50mg od if not tolerated	Tetracycline Reserved for treatment of NTM. **C*onsultant decision*.** Infusion over 60 minutes. Abdominal pain (commonly reported) may be indicative of pancreatitis. If pancreatitis develops stop tigecycline. Liver function tests, FBC, coagulation, amylase and lipase should be monitored at baseline then weekly during treatment. Nausea/vomiting a real problem. Use regular IV

			Ondansetron – ensure that patient receives anti-emetics **before** commencing treatment. Before using in children <12 years old, please confirm with dental professional all 'adult' teeth in place (due to discolouration of growing teeth/bone). Please notify consultant microbiologist when using tigecycline.
Tobramycin	IV	10mg/kg/day in ONE DOSE (Max 660mg/day) If previous course had raised trough level reduce dose by 20%. Note this dose is for CF patients only.	Aminoglycoside Infuse over 30 mins. Levels at 23 hours after 1st dose (*i.e.*, **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 Usual dilution: 0.9% sodium chloride. **DO NOT PRESCRIBE THIS DOSE FOR NON-CF CHILDREN.** Consent MUST be taken for use of IV aminoglycosides EVERY TIME GIVEN; and oral N-acetylcysteine (NAC) prescribed for all patients receiving IV aminoglycosides.

11.1e ANTIFUNGALS

Itraconazole	Oral	1month – 12 yrs: 5 mg/kg twice daily (max 200mg bd) >12yrs: 200 mg twice daily	**Almost never used at RBH** Poorly absorbed, use liquid, on empty stomach if possible. Capsules should be taken with acidic liquid *e.g.*, **Coca-Cola** and **food**. Stop PPIs 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. Levels should be monitored if efficacy is not observed, concerns about toxicity, or if an interacting drug is commenced. Pre-dose samples taken after at least 2 weeks on therapy. Aim: 0.5 - 2mg/L (parent molecule) and total (including active metabolite) of 1-4mg/l. Note itraconazole interacts with many drugs (including **ivacaftor, Orkambi** ,**Symkevi®, Kaftrio®** and **rifampicin)** so always check in BNFc and with pharmacist. Co-administration with Orkambi® **not** recommended – use alternatives. See section 6.4 for length of courses.

Posaconazole	Oral Suspension	6 months - 6 years: 200mg QDS 7 - 12 years: 300mg QDS Monitor levels. Monitor liver function tests monthly.	1st line for ABPA and aspergillus infection ***Consultant decision*** **(not licensed in <18 years old).** **The tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.** Tablets should be used preferentially as more consistent levels are obtained and the dosing regimen is less onerous. **Suspension** should be taken immediately following a meal (preferably fatty meal) to enhance absorption.
	Oral tablets	6 - 11 years: 300mg BD on day 1, then 300mg OD thereafter* ≥12 years: 400mg BD on day 1, then 400mg OD thereafter* *Note there is no need to wait 24 hours before administering daily maintenance dose. Monitor levels. Monitor liver function tests monthly.	Levels **when using suspension** reduced by ranitidine and proton pump inhibitors, which should be stopped if possible. **Tablets** can be taken with or without a meal. Levels should be monitored on initiation, on amendment of dosage, if an interacting drug is commenced or efficacy is not observed. **Pre-dose samples (trough)** taken after at least 1 week on therapy. Aim: 1 - 5mg/L For levels >5mg/L review dose with consultant and pharmacist. Note posaconazole interacts with many drugs (including **ivacaftor, Orkambi®, Symkevi®, Kaftrio®** and **rifampicin)** so always check in BNFc and with a pharmacist. See section 6.4 for length of courses.
Terbinafine	Oral	10 – 19kg: 62.5mg od 20 – 39kg: 125mg od 40kg +: 250mg od	For use in combination with an azole antifungal for *Lomentospora prolificans.* Consultant decision. Monitor liver function tests every 8 weeks when given in combination with an azole.

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 (3rd line) where patients have not responded to or are intolerant of posaconazole. ***Consultant decision*.** Take on an empty stomach. **Highly photosensitising** so warn patient re sunlight. High strength sunblock should be used in summer or on holidays for 4 weeks after course finished. Refer to dermatologist if photosensitivity reaction occurs. Risk of squamous cell carcinoma of the skin has been reported in long term use in patients with photosensitivity and other risk factors. Adrenal suppression has been reported in patients also taking inhaled corticosteroids. Levels should be monitored on initiation, on amendment of dosage, if an interacting drug is commenced or efficacy is not observed. Pre-dose samples taken after at least 3 days on therapy. Aim: 1.3 - 5.7mg/L Note voriconazole interacts with many drugs (including **ivacaftor, Orkambi** and **rifampicin)** so always check in BNFc and with a pharmacist. Monitor liver function tests + U&E's weekly for first month then monthly thereafter. See section 6.4 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, colistin. We NEVER use the standard amphotericin preparation (Fungizone) for IV use. Always prescribe using brand name. ***Consultant decision***. Administer over 30 mins. Compatible with 5% glucose only. Flush pre- & post dose with 5% glucose.

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. ***Consultant decision.*** Reduce dose in liver impairment (see BNFc). Infuse over 60 mins. Incompatible with glucose solutions.

11.1f CFTR MODULATORS

Ivacaftor	Oral	4 months and above: 5kg - <7kg: 25mg granules bd ≥7 - <14kg: 50mg granules bd ≥14kg - <25kg: 75mg granules or tablet bd ≥25kg: 150mg tablet bd	For children 4 months (and 5 Kg) and above with one of the following gating mutations- G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R or selected 'rare'mutations as approved by NHSE CFTR modulator commissioning policy. R117H 5T or 7T (not 9T) – post pubertal children • Must have clinical phenotype of CF and evidence of abnormal CFTR function (clinical or physiological). • We would not prescribe it to those with CFSPID. - Liver function tests (ALT, AST, total bilirubin) 3 monthly for 1st year then yearly (annual review). - Eye exams before starting then annually for all children <18 years. - Sweat chloride before starting then 6-8 weeks after starting (not mandatory). May be rechecked if concern about response / adherence. - Stool elastase in 2-5 year olds pre- and 6 months after starting. Take with fat containing food. • Sachet of granules should be mixed with one teaspoon (~5 mL) of age-appropriate soft food or liquid e.g., puréed fruits, yogurt, milk or juice. Once mixed, should be consumed within one hour. • Tablets must be swallowed whole and should not be chewed, broken or dissolved. • Doses should be given approximately 12 hours apart. Avoid food containing grapefruit. Always check for interactions when initiating treatment with ivacaftor or whenever new medicines are prescribed. See section 6.10 for specific drug interactions and Appendix 6 ;and refer to the paediatric pharmacy team for information. Dose may need to be reduced in hepatic impairment (see appendix 6)

Kaftrio® (ivacaftor/ tezacaftor/ elexacaftor)	Oral	6 years and above: <30kg: 2 Kaftrio (37.5/25/50mg) tablets in the morning **And** 1 ivacaftor 75mg tablet in the evening ≥30kg: 2 Kaftrio (75/50/100mg) tablets **And** 1 ivacaftor 150mg tablet in the evening	For children 6 years and above who are Phe508del heterozygous or children with selected 'rare mutations' as approved by NHSE CFTR modulator commissioning policy. -Liver function tests (ALT, AST, total bilirubin) 3 monthly for 1st year then yearly (annual review). - Eye exams before starting then annually for all children <18 years. - Sweat chloride before starting then 6-8 weeks after starting (not mandatory). May be checked if concerned about response and / or adherence. Take with fat containing food. • Tablets must be swallowed whole and should not be chewed, broken or dissolved. • Doses should be given approximately 12 hours apart. Avoid food or drinks containing grapefruit. Always check for interactions when initiating treatment with Ivacaftor or whenever new medicines are prescribed. See section 6.10 for specific drug interactions and Appendix 6; and refer to the paediatric pharmacy team for information. Dose may need to be reduced in hepatic impairment (see appendix 6)
Orkambi (Ivacaftor & Lumacaftor)	Oral	2 – 5 years: <14kg: Lumacaftor 100 mg/ivacaftor 125 mg sachets 1 sachet bd >14kg: Lumacaftor 150 mg/ivacaftor 188 mg sachets 1 sachet bd 6 – 11 years: Lumacaftor 100 mg/ivacaftor 125 mg tablets 2 tabs bd 12 years +: Lumacaftor 200 mg/ivacaftor 125 mg tablets 2 tabs bd Patients with very severe disease will	For children 2 years and above who are Phe508del homozygous - Liver function tests (ALT, AST, total bilirubin) 3 monthly for 1st year then yearly (annual review). - Eye exams before starting then annually for all children <18 years. - Sweat chloride before starting then 6-8 weeks after starting (not mandatory). May be checked if concerned about response and / or adherence. - Blood pressure before starting then periodically in clinic. Take with fat containing food. • Sachet of granules should be mixed with one teaspoon (~5 mL) of age-appropriate soft food or liquid e.g., puréed fruits, yogurt, milk or juice. Once mixed, should be consumed within one hour. • Tablets must be swallowed whole and should not be chewed, broken or dissolved. • Doses should be given approximately 12

		be admitted to hospital for initiation of Orkambi (to allow a min of 4 hours observation after first dosing). These patients will start on 1 tablet bd (half the usual dose) and be closely monitored before increasing to usual dose if tolerated. Rarely done as given to 2-5 y olds only	hours apart. Concomitant use of azole antifungals is not recommended due to Orkambi markedly reducing levels of these antifungals. Always check for interactions when initiating treatment with Orkambi or whenever new medicines are prescribed. See section 6.10 for specific drug interactions and Appendix 6; and refer to the paediatric pharmacy team for information. Dose may need to be reduced in hepatic impairment (see appendix 6)
Symkevi (Ivacaftor & Tezacaftor)	Oral	6 years +: <30kg: 1 Symkevi tablet (tezacaftor 50mg/ ivacaftor 75mg) in the morning **And** 1 ivacaftor 75mg tablet in the evening ≥30kg: Symkevi (tezacaftor 100mg/ivacaftor 150mg) 1 tab in the morning **And** 1 Ivacaftor 150mg tab in the evening	For children 6 years and above who are Phe508del homozygous or Phe508del heterozygous and have one of the following mutations: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T. Or children with selected 'rare mutations' as approved by NHSE CFTR modulator commissioning policy. - Liver function tests (ALT, AST, total bilirubin) 3 monthly for 1st year then yearly (annual review). - Eye exams before starting then annually for all children <18 years. - Sweat chloride before starting then 6-8 weeks after starting (not mandatory). May be checked if concerned about response and / or adherence. Take with fat containing food. • Tablets must be swallowed whole and should not be chewed, broken or dissolved. • Doses should be given approximately 12 hours apart. Avoid food or drinks containing grapefruit Always check for interactions when initiating treatment with Symkevi or whenever new medicines are prescribed. See section 6.10 for specific drug interactions and Appendix 6; and refer to the paediatric pharmacy team for information. Dose may need to be reduced in hepatic impairment (see appendix 6)

11.1g 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, erythromycin, fluconazole, ciprofloxacin – check BNFc
Azithromycin (see 11.1b for standard antibiotic doses)	Oral	10mg/kg od 3/week Once able to swallow tablets: 25-40 kg: 250mg od 3/week >40kg: 500mg od 3/week Mon/Wed/Fri	Potential long-term treatment as anti-inflammatory and prophylactic drug ***Consultant decision*** *Potential* for hepato- and ototoxicity but usually *very* well tolerated. Can cause tooth and tongue discolouration. **Avoid** long term concurrent use with erythromycin Can prolong QT interval. Do ECG before starting. Continue azithromycin prophylaxis during inpatient IV antibiotic courses (unless there is a suspicion of NTM).
Dornase alpha (RhDNase) Homecare delivery	Nebulised	2.5 mg once daily	Discuss timing with physio – usually in afternoon, at least 30 mins pre-physiotherapy. See section 6.6 for more details of variation of timing. Occasionally use twice daily for an acutely unwell child for a short course and must be reviewed at regular intervals for de-escalation to ONCE a day dose - ***consultant decision.*** Jet nebuliser, E-flow Rapid or I-neb (Green chamber if I-neb) Should be kept in the fridge. A single brief exposure to elevated temperatures up to 24 hours at up to 30°C does not affect its stability.

Hypertonic saline 3 or 7%	Nebulised	4 mls up to twice a day Immediately before or during physiotherapy.	Pre-treat with bronchodilator. (see section 6.7) Jet nebuliser, E-flow Rapid or I-neb (Lilac chamber if I-neb NB 2 fills per dose)
Mannitol (Bronchitol®)	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*** Commissioned for use in post-pubertal children provided NICE & NHSE criteria fulfilled. (see section 6.8). Doses should be taken morning and evening with evening dose taken 2 – 3 hours before bedtime. Tolerance should be assessed via 'Bronchitol Initiation Dose Assessment (BIDA)'
N-acetylcysteine (NAC)	Oral	< 12 years: 300mg BD ≥12 years: 600mg BD	Given for the duration of the IV aminoglycoside course. For the prevention of ototoxicity in patients receiving IV aminoglycosides. Available as 600mg capsules, 600mg tablets and 600mg effervescent tablets. • Effervescent tablets to be used in patients that cannot swallow tablets or where the dose needs to be given via enteral feeding tube. • Palatability of the effervescent tablets can be improved by adding some squash or non-acidic, non-fizzy juice/drink • Tablets (halved) to be used in patients who can take tablets but need a 300mg dose • Capsules/Tablets can be used for 600mg dose For use in DIOS please see section 11.2e

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.
- Creon preparations are porcine (pig) origin.
- Dose for a child established on pancreatic enzymes is *approximately* 1 capsule per 3-5 grams of fat.
- In babies, start with 1/3 to 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 are 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 (not enteric coated) = 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.

Patient/Parent/Carer advice available at -
https://www.medicinesforchildren.org.uk/medicines/pancreatin-for-pancreatic-insufficiency/

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 2016 are:

Age	**Vitamin A** *1 mcg = 3.3 IU*	**Vitamin D** *1 mcg = 40 IU*	**Vitamin E**	**Vitamin K**
< 1 Year	<450 mcg (1500 IU)	10 – 50 mcg (400 - 2000IU)	40 – 80 IU	< 2 years: 0.3mg/kg/day
1 - 3 Years	450 - 3000 mcg (1500-10,000 IU)	10 - 125 mcg (400 – 5000 IU)	50 – 150 IU	2 – 7 years: 5mg/day
4 – 7 years			150 – 300 IU	
>8 years			150 – 500 IU	5 – 10mg/day

Preparations:

- **DEKAs Plus** and **Paravit-CF** are brands of all-in-one multivitamins designed for people with CF containing vitamins A, D, E and K. DEKAs Plus also contains several other vitamins and trace elements.

- We **don't recommend using DEKAs Essential** as it contains less vitamin A and D than DEKAs Plus.

- Our first line all-in-one vitamin preparation is **DEKAs Plus** as it approved for use by the Advisory Committee on Borderline Substances (ACBS), so GPs are more likely to prescribe continuing supplies in the community.

- We offer DEKAs Plus to all newborn screened children (including those who are pancreatic sufficient). If children will not tolerate it, or if GPs are unable to continue supplies, then we will use Dalivit and vitamin E in infants.

- We will offer Paravit-CF to older children who do not tolerate DEKAs. Generally, though we use Paravit-CF for those with liver disease (defined as those on ursodeoxycholic acid).

- All patients initiating treatment with DEKAs Plus will be supplied with a supply letter outlining information about the preparations for the GP and community pharmacist.

- When increasing fat-soluble vitamin supplements, consider the risk of vitamin A toxicity, particularly for supplements containing high amounts of preformed vitamin A. Beta carotene is subject to negative feedback control and may be safer to use.

Vitamin	DEKAs Essential (per 1 ml)	DEKAs Plus Liquid (per 1 ml)	DEKAs Plus Chewable tab	DEKAs Plus Softgel	Paravit - CF Liquid (per 0.1ml)	Paravit-CF Capsule	Dalivit (per 1.2ml)
A	750mcg (250 mcg as retinyl palmitate; 500mcg as beta-carotene)	1,725mcg (225 mcg as retinyl palmitate; 1500mcg as beta-carotene)	5,450mcg (450 mcg as retinyl palmitate; 5000mcg as beta-carotene)	5,450mcg (450 mcg as retinyl palmitate; 5000mcg as beta-carotene)	480mcg (as retinyl palmitate)	1200mcg (as retinyl palmitate)	3000mcg (as retinyl palmitate)
D	2000 IU	750 IU	2000 IU	3000 IU	600 IU	1500 IU	800 IU
E	75 IU	50 IU	100 IU	150 IU	60 IU	150 IU	Nil
K	2mg	0.5mg	1mg	1mg	2mg	5mg	Nil

- 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 (4000 iu), vitamin D 10 mcg (400 iu)

- **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):

Should ideally be administered with Creon (if applicable) & food.

Birth to 12 months:
- Either **DEKAs** Plus Liquid 1ml od
- Or **Dalivit** 0.6 ml + **Vitamin E Liquid** 50 mg (0.5ml) od

1 to 4 years:
- Either **DEKAs** Plus Liquid 2ml od
- Or **Dalivit** 1.2 ml + **Vitamin E Liquid** 100 mg (1ml) od

5 to 8 years:
- Either **DEKAs** Plus Liquid 2ml od or **DEKAs** Plus Softgel or chewable tablet 1 od
- Or **Dalivit** 1.8 ml + **Vitamin E Liquid** 100 mg (1ml) od

9 years and above:
- Either **DEKAs** Plus 1-2 Softgel or 1-2 chewable tablets od
- Or **Vitamin A&D capsules** 2-3 + **Vitamin E (Vita-E Gel 75iu/400iu Caps)** 150 - 400iu.

Paravit-CF

0-12 months	Liquid 0.1 mls od
1-4 yrs	Liquid 0.25 mls od
5-8 yrs	Liquid 0.25 mls od OR Capsule 1 od
9 yrs+	Capsules 1-2 od

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)

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

Stoss therapy is the default therapy. It involves a single oral administration of the total treatment dose of vitamin D. An alternative is the whole dose as a single intramuscular injection but there is no reason to use this. This may need to be repeated if poor compliance persists with maintenance dosing. However, the Sydney paper (Shepherd et al, JCF 2012) showed this regimen maintained vitamin D levels for a year.

Oral colecalciferol **single dose**:
- 1 - 12 months 150,000 units
- 1 - 12 years 300,000 units
- ≥12 years 500,000 units

This is given as 50,000 units in 1 ml oral ampoule (Invita D3) and should be prescribed and supplied to patients from the hospital.

The previous regimen can still be used if there are difficulties with prescribing or tolerating high dose stoss therapy –

Oral colecalciferol for **3 months**:

- Infant 1 - 6 months 3000 units daily
- 6 months - 12 years 6000 units daily
- ≥ 12 years 10,000 units daily
- Alternative for older children – colecalciferol 20,000 units 3 times a week

This can be as

- colecalciferol liquid (Thorens®) 10,000 units/ml
- colecalciferol capsules 1,000 units
- colecalciferol capsules 10,000 (unlicensed) or 20,000 units

Vitamin K

We are now using **Paravit-CF** as the routine multivitamin for those with liver disease as it contains sufficient vitamin K that we do not have to prescribe separate menadiol or phytomenadione. This is given instead of DEKAs Plus. See above for dosing.

If there are significant clotting abnormalities and extra vitamin K is required use~~:~~ **Menadiol phosphate (water soluble) or Phytomenadione (fat soluble)** tablets (menadiol preferred when available). Menadiol can be dispersed in water if necessary.

Dose for 6 years & above: 10 mg od.

11.2 c 'Antacids'

If enzyme dose high and compliance and diet etc. have been assessed, then consider:

- **Oral omeprazole**:

	Once daily dose	**Maximum daily dose**	**Preparation for oral use** *(see below if via feeding tube)*
<2.5kg	0.7 - 1.4mg/kg	3 mg/kg/day	For doses <5mg use liquid formulation For doses 5 - 10mg use dispersible tablets
2.5 – 7kg	5mg	3mg/kg/day (max 10mg/day)	Use dispersible tablets **Or** If the dose is 10mg or 20mg use capsule (capsule can be opened and contents of capsule put on acidic fluid e.g., apple puree for
7-15 kg	10mg	20 mg daily	
>15kg	20mg	40 mg daily	

			administration)

- Doses may be divided and given twice daily if required.
- If using dispersible 'MUPS' tablets:
  - Round to nearest 5mg (half of a tablet).
  - Tablet can be cut in half 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.
- Alternatively, patients can open the capsule and swallow the contents with half a glass of water or after mixing the contents in a slightly acidic fluid *e.g.*, fruit juice or applesauce, or in non-carbonated water. If using this method, then doses should be rounded to nearest 10mg (whole capsule).
- If unable to tolerate omeprazole – lansoprazole can be tried as an alternative – see BNFc for doses.
- For administration through an *enteral feeding tube*:
  - Children aged >1 year (feeding tube French size ≥6) & ≥ 10kg – use esomeprazole G/R granules for suspension – see BNFc for doses.
  - Children aged >1 year & <10kg – use omeprazole liquid
  - Children aged <1y year (all feeding tube sizes) – use omeprazole liquid

11.2d Gastro-oesophageal reflux

Very common in CF.

- **Oral omeprazole**:see above (11.2c) for doses

Consider: **Infant gaviscon**, <4.5kg: 1 sachet per feed (max 6 doses/day); >4.5kg: 2 sachets per feed (max 12 doses/day).

Erythromycin dose for gastric stasis is: 3 mg/kg qds orally.

- Risk of cardiac adverse effects such as arrhythmias.
- A baseline ECG is recommended in patients concomitantly receiving drugs that increase QT prolongation.
- Subsequent 6 monthly ECGs should only be completed for patients at an apparent risk. (*e.g.*, cardiovascular instability)

11.2e Distal Intestinal Obstruction Syndrome (DIOS)

Old name meconium ileus equivalent (MIE). See **section 7.9 for treatment protocol.** All therapies are osmotic in action therefore fluid support is CRUCIAL, if necessary, intravenously.

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

Use for up to 3 days if no response in first 24 hours (but not if symptoms worsen).

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

- **Rectal gastrografin**
  - Same dose as oral, diluted as per formulary 11.2e. Consider rectal gastrografin if oral administration is not possible or if there is vomiting due to obstruction. This is rarely used and is a last resort. It can be administered **under radiological guidance to achieve a guided approach.** Watch for dehydration, a plain AXR at 1 hour may be required to exclude massive dilation. If the latter is present, urgent referral to a paediatric surgeon is required.

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

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

- **Polyethylene glycol** (**Klean-prep)**

  - **Do NOT give in the presence of bile stained vomiting.**
  - Solid food should not be given for at least 2 hours before starting treatment.
  - Add contents of 1 sachet to 1 litre water – can be flavoured with a clear fruit cordial. After reconstitution the solution can be kept in a refrigerator and discarded if unused after 24 hours.
  - Can be given orally or via NG tube (usually latter).
  - Do not administer just before bedtime due to risk of aspiration.
  - Patients must be reviewed after 1st 4 hours.
  - If not passing essentially clear fluid per rectum then a further 4 hour treatment can be given.
  - Monitor for hypoglycaemia, which can occur with CF diabetics undergoing this regimen.
  - 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.
  - Repeat 4 hour treatment if necessary.

- Where Klean-Prep is not available Moviprep may be used in its place. A litre of Moviprep consists of one 'sachet A' and one 'sachet B' dissolved together in water to make one litre of solution. ONE Moviprep (sachet A + B contains 100g Macrogol 3350) is roughly equivalent to TWO Klean-Prep (each sachet contains 59g Macrogol 3350).

- **Oral Picolax:** 1 - 2 years: 0.25 sachet STAT
  2 – 3 years: 0.5 sachet STAT
  4 – 8 years: 1 sachet STAT
  9 years and over: 1 sachet STAT

Can be repeated 6-8 hours later if necessary.

Prevention of DIOS:

N-acetylcysteine (oral)

<2 years: 100 – 200mg tds
2 – 11 years: 200mg tds
≥12 years: 200 – 400mg tds

11.2f Constipation

Ensure fluid intake is adequate.

Lactulose

<1 year	2.5 ml bd
1-4years:	2.5 – 10ml bd
>5years:	5-20 ml bd

then adjust dose according to response.

Movicol (Macrogol Compound Oral Powder)

Although the doses here refer to Movicol there are a number of other brands / generics available. Those equivalent to Movicol Paediatric include: Cosmocol Paediatric and Laxido Paediatric; equivalent to Movicol include Cosmocol and Laxido.

Chronic constipation, prevention of faecal impaction:

1 - 5 years: 1 sachet of Movicol **Paediatric** OD.
Adjust dose accordingly - maximum 4 sachets daily.

6 - 11 years: 2 sachets of Movicol **Paediatric** OD.
Adjust dose accordingly - maximum 4 sachets daily.

12 - 17 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** sachet in 1/4 of a glass (60-65ml) water and each Movicol sachet in 1/2 of a glass (125ml) water

11.2g Salt supplements

Salt supplements are available as a way of giving extra salt to children with CF. These are very effective when children are feeling tired or getting cramps due to hot weather.

- **Infants 0 – 12 months**: Up to 2 sachets of Dioralyte or an equivalent oral rehydration solution per day. Each Dioralyte sachet is mixed with 200mls of water (use cooled boiled water if under 6 months). Once made up, Dioralyte can be kept in the fridge for 24 hours.

This can be easier to achieve by giving 100ml twice a day to younger babies. For other oral rehydration solutions follow the manufacturers recommendations for the preparation and storage of solutions.

- **Children 1 - 7 years old**: 2 sodium chloride 600mg MR tablets (Slow Sodium, containing 10mmol sodium per tablet) per day during hot weather. For those who will not take tablets, Dioralyte or an equivalent oral rehydration solution can be used - usually 2–4 sachets per day.

- **Children over 7 years old**: 2 – 4 sodium chloride 600mg MR tablets (Slow Sodium, containing 10mmol sodium per tablet) per day during hot weather. Can also have Dioralyte or an equivalent oral rehydration solution.

11.2h Liver disease

Ursodeoxycholic acid: 10 – 15mg/kg bd oral.
There is no advised maximum dose, but our adult unit would go up to 500 mg 2-3 times daily.
Commonest side effect is diarrhoea (rare though), in which case, reduce dose. Last dose should be taken in late evening.

Vitamin K – given as **Paravit-CF** (see 11.2b).

11.2i Anti-emetics

A pre-emptive and stepwise approach is necessary in preventing the impact of emetogenic medicines such as tigecycline:

1st line: Commence regular Ondansetron IV 100mcg/kg (max 8mg) tds **before** starting treatment. Be aware it can be constipating, so if DIOS an issue ensure well hydrated and consider laxatives.

2nd line: If not controlled on above, consider adding regular domperidone PO 0.25mg/kg (max 10mg) tds

Note – both ondansetron and domperidone can prolong QT interval – baseline ECG should be carried out in patients concomitantly receiving drugs that increase QT prolongation.

3rd line: If nausea not controlled despite adequate doses of ondansetron and domperidone, or if above contraindicated, then add aprepitant 3mg/kg (max 125mg) on day 1 then 2mg/kg (max 80mg) on days 2 & 3. Stop after day 3 and reassess symptoms.

11.3 Home delivery of medicines

NHS England Prescribed Specialised Services Commissioning Intentions (2014) states that the hospital trust has responsibility for the ongoing prescription of high cost inhaled medicines (dornase, tobramycin, colistin, aztreonam lysine, mannitol) for cystic fibrosis. This

is also the case for CFTR modulator therapies (ivacaftor, Kaftrio, Orkambi, Symkevi). At RBH these medicines are supplied to patients using homecare delivery services. These homecare services enable these medicines that are not able to be prescribed by the patient's GP, to be prescribed by the CF team at RBH, and then delivered directly to the patient at home by the hospital's chosen homecare providers, for as long as is required. The default for prescribing and supply of **all other** CF medicines except the ones listed above should be from the GP. Note if we prescribe from our pharmacy there is an extra 20% cost for VAT; if home prescribed then there is no VAT payable, so this is the preferred option.

If homecare is required, then please contact a member of the paediatric pharmacy team as soon as possible (Bleeps 7403/7410/7425/7428 or ext. 84375; paediatricpharmacy@rbht.nhs.uk (internal email only); rbh-tr.paediatricpharmacy@nhs.net) 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 1 - 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

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 I Clinic Date …../…../….. Attended: Yes ☐ No ☐
- ***i.*** *If NO, action taken:*

c. Pre-Transition 2 Clinic Date …../…../….. Attended: Yes ☐ No ☐
- ***i.*** *If NO, action taken:*

d. Transition Clinic Date …../…../….. 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 Non-tuberculous 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 Liver disease Oesophageal varices CF Related Diabetes Arthropathy Severe small airways disease Other associated conditions	**Details**			
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?	

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 ☐

SOCIAL CARE INVOLVEMENT

Named social worker:

Contact details:

Last contact date:

Attach any additional information/report 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

Paediatric Clinic - Form completed by: Date:

	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 Registry 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:

Adult Clinic - Form completed by: Date

Daniel Office – Clinical Nurse Specialists (d.office@rbht.nhs.uk)

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

Dr Andrew Jones - Consultant Physician (a.jones2@rbht.nhs.uk)

Please send a copy attaching a referral letter if the patient is outside the Royal Brompton Hospital:

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

Appendix 2 - Risks of getting *P. aeruginosa* from the environment

This has been published – Balfour-Lynn IM. J Cystic Fibrosis 2020;20:17-24.

We understand that many parents are very concerned about their child 'catching' or acquiring *Pseudomonas aeruginosa* (PsA) from the environment. We realise this is a personal issue and that different families view things differently, especially in terms of balancing risk *vs* benefit. Parent's views may also change with time *e.g*., as their child gets older or depending on how well their child has been.

In order to ensure a consistent message, we have written this guide, which is a consensus view from the Brompton paediatric team and follows a comprehensive literature search. In some cases, there is strong research evidence, and we can be firm in our views. However, for many situations, the evidence is lacking or itself inconsistent. In those instances, parents will need to decide for themselves what to let their child do and decisions are often best made using common sense.

The UK CF Trust state 'It's important to remember that life can be risky – we all have to weigh up risk against quality of life.' We agree with this and would like children to lead as normal a life as possible, and not miss out on fun activities at home or school.

It is impossible to avoid contact with PsA, it is everywhere, and water is its natural environment. The risk of PsA acquisition is greater if PsA is present in water that is aerosolised (converted into a fine spray or mist), so it can be inhaled directly into the lungs. There is a small risk, but it is still possible, for a child to have PsA on their hands and put their fingers in the nose or mouth and hence inhale it. There is a dose effect, so the longer the exposure or the higher the bacterial content, the more likely the bacteria will be acquired and stay in the lungs. It is difficult to know whether drinking PsA-contaminated water affects the lungs as PsA can be found in stool samples in many healthy people. Always remember that other people with PsA infection are a potential source, and close contact with them puts children with CF at risk of infection.

We have focussed this guide on PsA, but obviously there are other organisms acquired from the environment that can be a problem, these are mentioned within the main guidelines where appropriate. These guidelines still apply to children who have already isolated PsA; it is possible to acquire more than one strain.

Things to definitely avoid

- **Hot tubs, Whirlpools, Spa pools, Jacuzzis, Hydrotherapy pools**
  There is strong evidence of the presence of PsA in warm water that is aerosolised and easily inhaled with the person's head just above the water; and reported cases of acquired infection in adults with CF. PsA has been isolated from culture plates held 15 cms (6 inches) above the water surface when the tub was turned on. A 2018 Northern Ireland study found PsA in 21% of 243 hot tubs and 7% of 5811 Jacuzzis There is guidance to reduce survival and growth of PsA in these environments (*e.g*., levels of free chlorine and bromine, pH of water) but we still recommend total avoidance.

- **Tropical greenhouses, butterfly houses**
  Misting systems to water plants in tropical greenhouses and butterfly houses have been shown to contain PsA so are a risk as the fine water droplets are easily inhaled.

- **Outdoor misting systems**
  Some restaurants or other public areas have an outdoor misting system that sends a spray of mist downwards to keep people cool. We can find no evidence but there is a theoretical risk that the mist may contain PsA from the local water supply.

- **Squirting bath toys**
  Bath toys that have a valve on the base (*e.g.*, plastic ducks) or that can squirt out water can be a problem if the water sits inside the toy for a long time, as they cannot be fully emptied and dried. There is evidence of a PsA outbreak on a children's cancer ward that originated in the toy box containing water-retaining bath toys. The same would apply to any hollow bath toy that retains water.

- **Swimming in stagnant ponds & canals** (see below).

- **Fish tanks (especially warm tanks for tropical fish)**
  Organisms have been isolated from fish tanks and cases reported of infection in people with CF. We believe they should be avoided. However, the US guidelines [1] simply suggest that gloves should be worn when cleaning out a fish tank.

- **Compost** (heaps and bags)
  Compost is essentially decayed vegetation, and is like enriched soil, but it can contain *Aspergillus* spores, and bacteria such as *Pseudomonas* species. It should definitely be avoided due to the particularly high risk of *Aspergillus*.

- **Mucking out stables**
  This is particularly bad for potential contamination with *Aspergillus*. A warm mucky stable is also likely to be a source of PsA as well.

<u>Things to take precautions with but allow</u>

- **Digging in the garden soil, playing in the park, playing outdoor sport**
  PsA is known to reside in soil, although interestingly despite this fact being frequently quoted, publications suggest PsA is infrequently cultured. A 1974 study in 58 agricultural sites in California found that a quarter of soil samples grew PsA (especially in soils where tomatoes were grown). However, many studies since have found it to be rarely detected (*e.g.*, a 2014 study of 380 samples from France & Burkina Fasu). Soil that is contaminated by organic fertiliser or animal manure is best avoided. Any PsA present in someone's garden is only a potential source of infection if the child puts the soil on their face and specifically up their noses or in their mouths (from contaminated fingers). We therefore suggest playing in the garden or park should not be stopped, as long as the children's hands and face are cleaned properly afterwards. The same applies to older children playing outdoor team sport (football, rugby etc.) which we encourage as exercise is so beneficial. We believe running through piles of damp leaves (or collecting leaves) would also seem to be safe. The US guidelines suggest that people with CF should limit prolonged exposures to activity that generates dust from the soil or organic matter *e.g.*,

lawn mowing to decrease exposure to *Aspergillus* and *B cepacia.* If a child wants to 'garden' they could always wear gardening gloves.

Proper hand washing is imperative. That is not always possible when outside the home, so parents (and older children) may wish to carry small bottles/tubes of antibacterial gel (hand sanitisers) that can be bought in chemists and supermarkets.

- **Mud kitchens**
  These are toy kitchen units made of wood, plastic and metal, where mud is used as the ingredient for all the food being made so gets all over the children's hands and probably faces! The same applies as digging in the garden, any PsA in the mud will not be aerosolised, so as long as the children's hands and face are cleaned properly afterwards, we believe the risk is minimal. There is no published evidence to further guide us.

- **Muddy puddles**
  Mud is a mixture of compressed soil and water; a puddle that has dirty stagnant water in it may contain many bacteria. A 2018 study in Northern Ireland sampled 18 freshly formed puddles in two hospitals, and 8 puddles from two countryside locations. Many bacteria were isolated, more often from the hospital locations. The commonest type were gram-negative organisms, and particularly *E.coli*. PsA was isolated only from one hospital puddle (and was a type not found in any CF patient in N. Ireland; there were three other types of Pseudomonas found in the countryside and hospital. However, if a child steps in it or even splashes in it, the water is not aerosolised sufficiently to be inhaled so we believe this is not a significant risk and need not be avoided. Pavement puddles dry so fast that the water does not stagnate and is also not in contact with soil/mud, so is perfectly safe to splash through.

- **Sandpits**
  Sand can be contaminated with PsA and it has been occasionally isolated from some beaches (probably due to human contamination in the sea). In a sandpit with clean dry sand the risk is minimal, although the sand is often damp; nevertheless, we believe the risk is only significant in a sandpit with free standing stagnant water. So, we suggest sandpits are fine if there is no visible standing water; this will be easier to control in someone's own garden. It is worth keeping a lid on the sandpit to reduce the amount of rainwater that might collect. Also, when filling up the sandpit from large bags, the sand is usually wet in the bag and should be left to dry out before use. The CF Trust advises schools that the sand should be regularly changed although do not say how often. A sandpit in a park is less likely to be clean, but by far the most frequent contaminant is *Toxocara* from cat and dog faeces.

- **Swimming**
  It is important children learn to swim for safety reasons. PsA is an aquatic organism preferentially living in water habitats and colonising moist environments. The water will not be aerosolised (apart from waterfalls), so it is unlikely to be an issue if it is not inhaled. Washing afterwards is obviously a good idea. **Inflatable toys** should be dried out after use, and not be left to hold stagnating water.
  - **Sea** – PsA has been grown out in the open ocean. However, sea water by a beach is most likely contaminated from human faeces. It is worth checking the cleanliness of beaches which can be done online for UK beaches (https://www.gov.uk/quality-of-local-bathing-water). We suggest swimming in the sea is fine.

- **Lakes** can also be contaminated in a similar way to the sea but again we do not believe this is a problem.
- **Rivers** – even rivers have isolated PsA but again we would not discourage swimming in a river (if it is deemed safe for bathers).
- **Ponds** – this is more likely to be a problem in a small stagnant pond due to rotting vegetation *e.g.*, leaves. In that case it should be avoided, although is likely to be safe in a large pond that looks clean.
- **Canals** – similarly to the ponds, the water is often stagnant and usually looks dirty. We would suggest avoiding this.
- **Swimming pools** – if the pool is disinfected (usually with chlorine) to recommended levels then this should not be a problem, although PsA has been isolated occasionally from both indoor and outdoor public pools. Caution though with hotels and renting holiday villas with private pools in case the pool is not treated properly. It is safest for people with CF to only use pools that are well maintained and have an associated quality assurance monitoring programme to eliminate PsA.

- **Paddling pools**
  These will be fine if they are emptied after each use & dried out, then filled up again with fresh water when they are to be reused.

- **Clay**
  Modelling clay usually comes in a bag and is wet, often with loose water at the bottom of the bag. The clay should be allowed to dry out first although needs to be moist for it to be usable.

- **Water amusement parks**
  The water will be aerosolised and on some rides, spray can be inhaled. However, if the facility uses treated disinfected (usually chlorinated) water to industry standards this should be safe and can be checked in advance.

- **Play fountains** (water that spouts up from pavement jets)
  Some of the water is likely to be aerosolised so does present a risk. However, if the fountains are chlorinated (like in a swimming pool), they should be safe.

- **Pond-dipping**
  This is collecting pond life in a jar attached to a net that is dragged through the water. It is likely that the pond water (that may be stagnant) will get on the children's hands and of course may end up being flicked around when an adult is not looking, especially when there are a lot of children taking part. It is likely to be safe if it is supervised properly, and the child cleans their hands properly afterwards. There is no evidence to guide us, and it is difficult to know what is best, so parents will have to decide whether they believe it to be a sufficient risk to stop the child joining in.

- **Touch pools in a public aquarium**
  It is most likely that there will be bacteria in the water, including non-tuberculous mycobacteria. However, the water will not be aerosolised, and there are good hand-washing facilities on the spot, so we believe the children can take part as long as they definitely clean their hands well and are supervised carefully.

- **Petting zoos and farm visits**
  Clearly stagnant water or small ponds should be avoided. Caution also in chicken coops, stables and contact with mouldy hay for *Aspergillus*. Hand hygiene is important after stroking the animals and most places will have hand washing facilities for all the children anyway. There have been no reports of transmission of pathogens from farm animals or pet therapy animals to people with CF, although animals are a potential source of several types of infection (*e.g.*, PsA from horses, MRSA from pigs).

- **Caves**
  These are often damp environments with water dripping down the sides of the walls. The water is not aerosolised, and the child will not be in direct contact with the water. There is no evidence to guide us, but we believe a visit to a cave need not be avoided.

- **Snow**
  A 2018 study analysed fallen snow from 37 sites in parks, gardens, public open spaces and footpaths. Although bacteria were detected in the majority of samples, PsA was not detected in any. Caution should be taken in dirty slushy melted snow especially lying over mud, but there should be no harm in playing in fresh white snow.

- **Showers**
  The shower heads can be a source of PsA with colonised biofilms, and the shower spray contains aerosolised droplets that can be inhaled. It is best to run the shower for 1-2 minutes before the child gets in.

- **Sink and bath taps**
  These can also contain PsA (in the form of biofilms), but the risk is reduced compared to showers as the water spray is not being inhaled. If the tap is in frequent usage the risk is also lessened but taps that are rarely used should have the water run through them for 1 minute every day. This is unlikely to be an issue in someone's home. PsA is most often detected from kitchen and bathroom drains in homes of people without CF; and from shower and bathroom drains in homes of people with CF.

- **Water pistols and 'super-soakers'**
  Similarly, to squirting bath toys, this could be a problem if the water is kept inside the toys for a long time. A forceful super-soaker could aerosolise the water and can be squirted in the face. However, we suggest as long as they are emptied fully after use and dried out they can still be played with. **Water play** should be safe if the water is fresh and has not sat stagnating in containers; toys should be dried out at the end.

- **Flower vases**
  Water should be changed before it smells and trim the leaves off stems so that they do not sit in the water.

- **Humidifiers & vaporisers**
  Water sits in a reservoir which is evaporated and blown into the air. If the reservoir is kept clean, and fresh water put into it before use, it should be safe, but do not use it if the water has been stagnating in the reservoir for a while. Also, never add disinfectant to the water – some have caused harmful interstitial lung disease.

- **Air conditioning**
  No evidence on this but these should best be avoided if the units are dripping water.

- **Flushing toilets**
  Aerosols containing bacteria, including PsA, can be created when flushing toilets, so the lids should be lowered before flushing.

<u>Things that must not be avoided</u>

- **Dentist**
  There has been concern expressed in the past about aerosolisation of PsA-contaminated water from dental chair units. PsA may get there from municipal water or the suck back of a patient's saliva into the line due to lack of anti-retraction valves. It is critical that children with CF attend the dentist regularly, especially given the effect of some of the antibiotics and the potential high sugar diet. Furthermore, rotten teeth can promote PsA in the mouth which can infect the airways.

- **Drinking water**
  PsA has been isolated in tap water, well water, drinking water dispensers (coolers), water from vending machines, bottled water, and even distilled water. There is no evidence that drinking water with the low levels of PsA found will cause lung infections, and high levels are required to colonise the gut. Drinking water need not be avoided, nor need the water be boiled first. The US guidelines suggest that tap water or well water that meets local public health standards may be used for drinking.

  Many people use refillable water bottles. Mostly the filters are not antibacterial but are carbon filters to remove chlorine and improve the taste. Certain designs mean that the filters remain wet, possibly even holding water, so these should be avoided. Similar advice is given for water jugs with filters. Bottles with antibacterial filters do exist (for camping etc.) but again it is important to know if the filter remains wet and possibly holds on to the bacteria, in which case they should be avoided.

[1] *Saiman et al. Infection prevention & control guidelines for cystic fibrosis: 2013 update. Infect Control & Hosp Epidemiol 2014;35:S1-S67.*

Appendix 3 – CF Pre-admission plan

USE STICKER

Patient Name:	Hospital No:
DOB:	NHS No:

TIMING of admission

☐ Urgent <24 hours
☐ Soon <1 week
☐ Routine <4 weeks
☐ Planned future date (give date) -

REASON for Admission

☐ Chest exacerbation for IV antibiotics
☐ Routine 3 monthly IV antibiotics
☐ Nutritional review
☐ Other (give reason) –

Decision to admit date:	Planned date of admission:
Actual date of admission:	Predicted duration:
Discharge plans (Stay RBHT / Home IVABs / local hospital)?	

ANTIBIOTIC PLAN

If required, which IV antibiotics to be given -

IV Access

Portacath yes / no
PICC yes / no. If yes, requested on ICE? yes / no
Entonox yes / no
Sedation yes / no
GA yes / no. If yes, for blind BAL? yes / no. If yes, inform physiotherapist? yes / no

Special procedures or investigations
(*e.g.*, annual review, CGMS, CT scan, bronchoscopy)

Any other important information

Segregation issues
☐ *Burkholderia* spp.
☐ *M. abscessus*
☐ MRSA
☐ Multiresistant PsA
☐ Other -

NAME of person arranging admission -

SIGNED: DATE:

Appendix 4 –
Paediatric cystic fibrosis intravenous aminoglycoside consent form

The following information explains the aims, benefits, and risks of aminoglycoside antibiotics.

What are intravenous (IV) aminoglycosides?
Aminoglycosides are antibiotics (given into a vein), used in children with cystic fibrosis (CF), to treat serious lung infections caused by bacteria such as *Pseudomonas aeruginosa* and *Mycobacterium abscessus* complex. The aminoglycoside antibiotics we use are tobramycin and amikacin.

Reasons for starting aminoglycoside therapy
Both *Pseudomonas* and *Mycobacterium abscessus* complex infections are hard to eradicate and require treatment with more than one antibiotic. There is strong evidence that aminoglycosides are one of the most effective types of antibiotics for children with CF, so it is our standard practice to use them. This is in line with recommendations from both the UK CF Trust and the European Cystic Fibrosis Society. We use these antibiotics when we believe the potential benefits of this treatment outweigh the risks, which are outlined below.

Side effects
Like many important medicines, aminoglycosides have side effects and can affect your child's kidneys and hearing, and therefore we always monitor drug levels in your child's blood to minimise the possibility of these occurring.

Although theoretically this is possible with a single aminoglycoside course, it is usually the accumulation of many courses (usually over several years), that increases the risk of hearing problems, even if every blood test for the drug concentration was within the normal range.

It should be emphasised that the possibility of significant hearing problems is small, even with many aminoglycoside courses. Some children may be more sensitive to these antibiotics than others, but this is still a new area of research.

Monitoring
Regular blood tests (weekly) will be done to ensure that the correct dose of antibiotic is given to help minimise the risk of side effects.

We will also arrange for children to have a baseline hearing test at their local hospital if they need amikacin for *Mycobacterium abscessus* complex infections; or are starting regular 3-monthly courses of IV antibiotics, and this will be repeated every year or sooner if concerns arise.

If symptoms such as hearing difficulties, tinnitus (ringing sound in the ears), dizziness or problems with balance are noticed, please tell your doctor as soon as possible. We will be monitoring for kidney problems, but it is most important to stay well hydrated (drink plenty) especially in hot weather. If there are concerns, we will stop the aminoglycosides and use an alternative antibiotic, although the alternative antibiotics may not be quite as effective in treating the infection.

Child or Parent/Carer name **Child or Parent/Carer signature**

…… ……..……

Date……

I agree to the treatment outlined above and have read and understood the information given to me and my questions have been answered.

Interpreter name **Interpreter signature**

..……. ……

Date.……

I have explained the information above to the patient/parent/carer to the best of my ability and in a way in which I believe he / she can understand.

Doctor name **Doctor signature**

.. …… **…….**

Date …….

I have discussed the side effects with the patient and answered his / her questions.

Patient / parent / carer has given consent to treatment with IV aminoglycosides □

Patient / parent / carer has declined treatment with IV aminoglycosides □

Copy into patient notes
Copy given to patient/parent/carer
Copy into Audit Folder

October 2016

Appendix 5 – Letter for eye testing prior to starting CFTR modulators

Royal Brompton Hospital
Sydney Street
London SW3 6NP

Main switchboard: +44 (0)20 7352 8121

Date:

Dear Optometrist,

This child has been referred to you for an ophthalmological examination as he/she is currently prescribed a medication called a CFTR modulator which is a treatment for cystic fibrosis. Baseline and follow-up ophthalmological examinations are recommended in paediatric patients initiating these treatments to look for lens opacities.

There have been cases where non-congenital lens opacities without impact on vision have been reported in paediatric patients treated with a CFTR modulator. Although other risk factors were present in some such as corticosteroid use and exposure to radiation, a possible risk attribution to treatment cannot be excluded.

CFTR Modulator treatments are Ivacaftor, Orkambi, Symkevi and Kaftrio

Please could you check and assess for: **Opacities and cataracts**
This examination will need to be done on an annual basis.

Please provide the patient or their carer with a copy of the assessment report from your consultation so that it can be added to their medical record.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search MHRA Yellow Card in the Google Play or Apple pp Store. Adverse events should also be reported to Vertex Pharmaceuticals (UK) Ltd on 0800 0282616 or +44 (0) 20 3871 877

Thank you for your help, please contact us if there are any further queries.

Many Thanks

Paediatric Cystic Fibrosis Team
0207 351 8755

Appendix 6 – CFTR modulator drug interactions

April 2021

CFTR Modulators: Interactions & Liver impairment in children

Royal Brompton and Harefield NHS Guy's and St Thomas' NHS Foundation Trust

	Orkambi	Symkevi	Kaftrio	Ivacaftor
Weak or moderate CYP3A inhibitors (e.g. fluconazole, isavuconazole, erythromycin)	No dose adjustment of Orkambi required but higher dose of **CYP3A inhibitor** may be required to obtain desired clinical effect. Ideally use alternative. If this is not possible consider stopping Orkambi whilst on treatment, restarting after washout period: • Fluconazole: 6 days • Isavuconazole: 23 days • Erythromycin: 1 day	• Alternate ONE Symkevi tablet and ONE Ivacaftor tablet every morning • No tablet in the evening • Resume standard Symkevi/ivacaftor dosing after washout period: ○ Fluconazole: 6 days ○ Isavuconazole: 23 days ○ Erythromycin: 1 day	• Alternate TWO Kaftrio tablet and ONE Ivacaftor tablet every morning • No tablet in the evening • Resume standard Kaftrio/ivacaftor dosing after washout period: ○ Fluconazole: 6 days ○ Isavuconazole: 23 days ○ Erythromycin: 1 day	• One Ivacaftor tablet every morning • No tablet in the evening. • Resume standard ivacaftor dosing after washout period: ○ Fluconazole: 6 days ○ Isavuconazole: 23 days ○ Erythromycin: 1 day
Strong CYP3A inhibitors (e.g. itraconazole, posaconazole, voriconazole and clarithromycin)	No dose adjustment of Orkambi required but higher dose of **CYP3A inhibitor** may be required to obtain desired clinical effect. Ideally use alternative. If this is not possible consider stopping Orkambi whilst on treatment, restarting 7 days after treatment has stopped	• ONE Symkevi tablet twice a week (taken approximately 3-4 days apart) • No tablet in the evening • Resume standard Symkevi/ivacaftor dosing after washout period: ○ Itraconazole: 9 days ○ Posaconazole: 7 days ○ Voriconazole: ~2 days ○ Clarithromycin: 2-3 days	• TWO Kaftrio tablets twice a week (taken approximately 3-4 days apart) • No tablet in the evening. • Resume standard Kaftrio/Kalydeco dosing after washout period: ○ Itraconazole: 9 days ○ Posaconazole: 7 days ○ Voriconazole: ~2 days ○ Clarithromycin: 2-3 days	• ONE ivacaftor tablet twice a week (taken approximately 3-4 days apart) • No tablet in the evening. • Resume standard ivacaftor dosing after washout period. ○ Itraconazole: 9 days ○ Posaconazole: 7 days ○ Voriconazole: ~2 days ○ Clarithromycin: 2-3 days
Strong CYP3A inducer (e.g. rifampicin, rifabutin, phenytoin & St John's wort)	Co-administration with strong CYP3A inducers is not recommended. Use alternatives.			
Hormonal contraception	Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi	Symkevi and ivacaftor are not expected to modify the efficacy of hormonal contraceptives.	Kaftrio is not expected to modify the efficacy of hormonal contraceptives. For patients taking hormonal contraceptives who develop rash, interrupting treatment with Kaftrio and hormonal contraceptives should be considered.	Ivacaftor is not expected to modify the efficacy of oral hormonal contraceptives.

April 2021

CFTR Modulators: Interactions & Liver impairment in children

Royal Brompton and Harefield NHS Guy's and St Thomas' NHS Foundation Trust

Child-Pugh Score

Child Class A: >7 points **Child Class B: 7 - 9 points** **Child Class C: 10 - 15 points**

	1 point	2 points	3 points
Bilirubin -Total	<34.2µmol/	34.2-51.3 µmol/	>51.3 µmol/
Albumin	>35 g/L	28-35 g/L	<28 g/L
INR	<1.7	1.7-2.2	>2.2
Ascites	Absent	Slight	Moderate
Encephalopathy	No encephalopathy	Grade 1-2	Grade 3-4

	Orkambi	Symkevi	Kaftrio	Ivacaftor
Mild hepatic impairment (Child-Pugh Class A)	No dose adjustments			
Moderate hepatic impairment (Child-Pugh Class B)	1 sachet every 12 hours on alternate days **OR** 2 tablets in the morning and 1 tablet in the evening	• ONE Symkevi tablet each morning • **No** tablet in the evening	Use not recommended. However, if benefit exceeds risk: • Alternate Kaftrio tablets TWO each morning with ONE in the morning. • **No** tablet in the evening	Reduce to OD dosing
Severe hepatic impairment (Child – Pugh Class C)	1 sachet a day **OR** 1 tablet every 12 hours	If benefit outweighs risk, consider • ONE Symkevi tablet each morning • **No** tablet in the evening	Use not recommended	Reduce to alternate day dosing

What to do if a patient has raised liver function tests?

If any of the following:

- ALT or AST >5 x the upper limit of normal (ULN)
- ALT >3 x ULN with bilirubin >2 x ULN
- AST >3 x ULN with bilirubin >2 x ULN

- Consider withholding CFTR modulator and monitor LFTs closely until the abnormalities resolve
- Following resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered.

Orkambi and PPIs (e.g. omeprazole and lansoprazole)

- The effect of PPIs may be reduced by Orkambi
- Continue current PPI dosing but inform patient/family to look out for any increase in reflux symptoms
- If increased reflux symptoms, ensure PPI dosing is optimised to maximum dosing
- Omeprazole maximum daily dosing
  - 2–17 years (Weight: 10–19 kg): 20mg OD
  - 2-17 years (Weight: >20kg): 40mg OD
- Lansoprazole maximum daily dosing
  - Weight up to 30kg: 1mg/kg (max 15mg OD)
  - Weight >30kg: 15-30mg OD

Appendix 7 - Drug Response Assessment testing

DRUG RESPONSE ASSESSMENT TESTING PROFORMA

*******THE TEST WILL NOT BE UNDERTAKEN WITHOUT ALL SHADED AREAS COMPLETED******

APPROPRIATE PRESCRIPTION ATTACHED? ☐

PATIENT NAME: **DOB:** **HOSPITAL NO:** **PATIENT WEIGHT:**	**Inpatient/ Outpatient**
DATE OF REFERRAL: **REASON FOR REFERRAL:** **PRESCRIBER: *PRINT*: ……** ***SIGN*……** **PRESCRIBER BLEEP/ EXT no. #** **CONSULTANT:**	**ALLERGIES**

Terminal clean required post-test? *(i.e. MRSA/ M. abscessus/B. cepacia)*: **YES / NO**

	Medicine	DOSE	Administered?	Initials for check
MEDICATION FOR TEST DOSE			**YES NO**	
Diluent (e.g. 0.9% saline for Colistin/Amikacin etc)				
PRE TEST BRONCHODILATOR ***(if part of patient usual regime)***			**YES NO**	
POST TEST BRONCHODILATOR ***(please circle/indicate dose)***	**Salbutamol NEB** **INHALER**	**……mg** **……puffs**	**YES NO**	

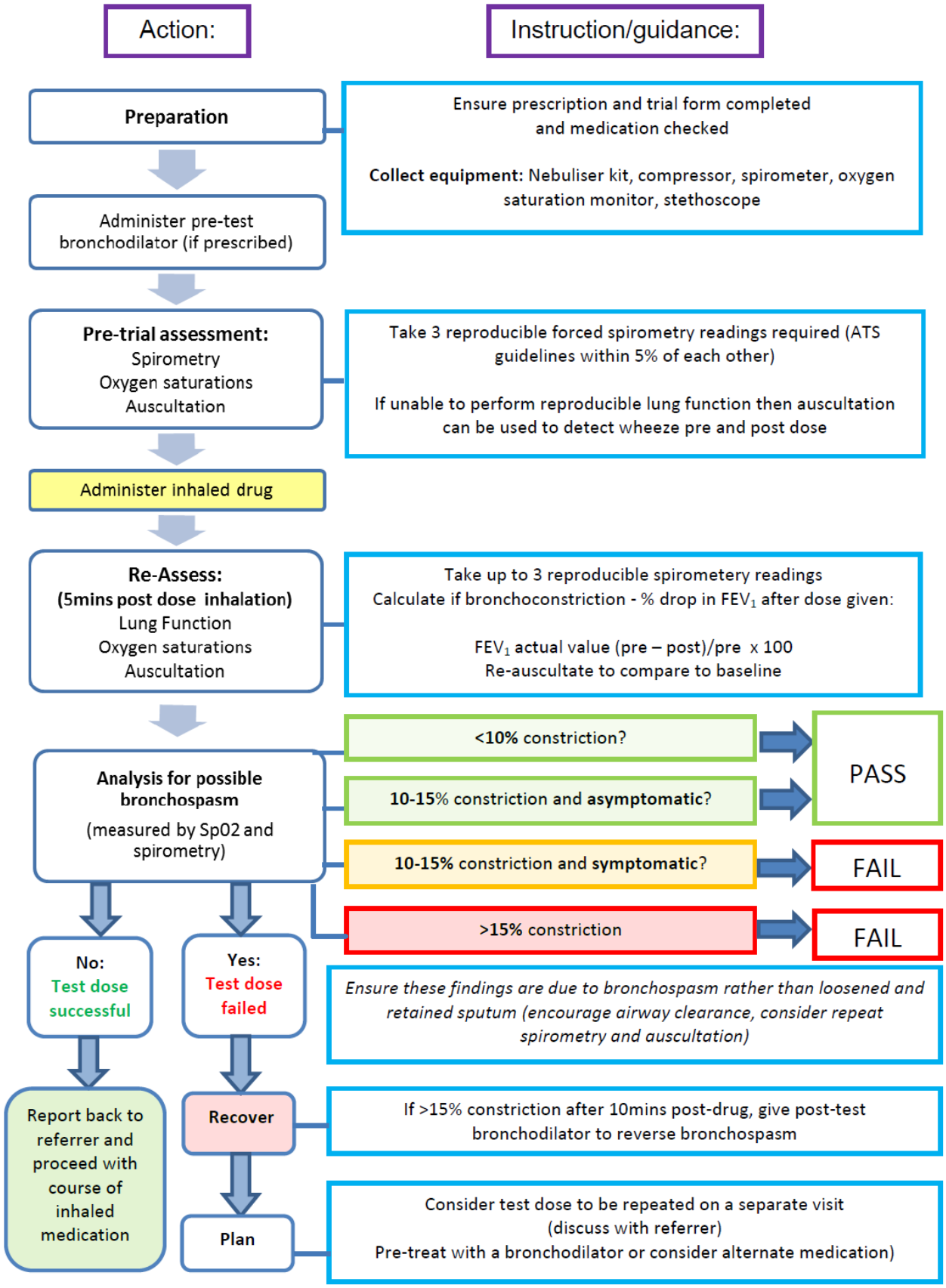
TO BE COMPLETED BY PHYSIOTHERAPIST:

DATE OF TRIAL…… **SPIROMETRY APPROPRIATE?: YES NO**
DEVICE USED? ……
TRIAL NOT COMPLETED? Why……

	FEV_1		Sp02	Other (e.g. ausc/HR)
PRE test	**L/min**	**% pred.**		
POST test	**L/min**	**% pred.**		
% change	*(see guidance attached)*			
Symptoms/ comments				
10 mins post ***(if needed)***	**L/min**	**% pred.**		
% change				
Symptoms/ comments				

Inhalation technique discussed (i.e. DPI)
Explained potential adverse events ☐ **Equipment explained/issued** ☐

Safe for Use: Yes / No Therapist signature_____ **Date**_____


Action:
Instruction/guidance:
Preparation
Ensure prescription and trial form completed and medication checked
Collect equipment: Nebuliser kit, compressor, spirometer, oxygen saturation monitor, stethoscope
Administer pre-test bronchodilator (if prescribed)
Pre-trial assessment:
Spirometry
Oxygen saturations
Auscultation
Take 3 reproducible forced spirometry readings required (ATS guidelines within 5% of each other)
If unable to perform reproducible lung function then auscultation can be used to detect wheeze pre and post dose
Administer inhaled drug
Re-Assess:
(5mins post dose inhalation)
Lung Function
Oxygen saturations
Auscultation
Take up to 3 reproducible spirometery readings
Calculate if bronchoconstriction - % drop in FEV1 after dose given:
FEV1 actual value (pre – post)/pre x 100
Re-auscultate to compare to baseline
Analysis for possible bronchospasm
(measured by Sp02 and spirometry)
<10% constriction?
10-15% constriction and asymptomatic?
PASS
10-15% constriction and symptomatic?
FAIL
>15% constriction
FAIL
No:
Test dose successful
Yes:
Test dose failed
Ensure these findings are due to bronchospasm rather than loosened and retained sputum (encourage airway clearance, consider repeat spirometry and auscultation)
Report back to referrer and proceed with course of inhaled medication
Recover
If >15% constriction after 10mins post-drug, give post-test bronchodilator to reverse bronchospasm
Plan
Consider test dose to be repeated on a separate visit
(discuss with referrer)
Pre-treat with a bronchodilator or consider alternate medication)

Appendix 8 - Guide for parents starting a child on a nebulised therapy

Helping a young child get used to nebulisers

Getting used to the nebuliser …. a staged approach

You will be given your mask and nebulising equipment at your appointment.

Sometimes it can take children some time to get used to wearing the mask and having a nebuliser. If your child is struggling the following tips can help them with this.

Stage 1

Play with the mask on a doll or a toy, or on 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.

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 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 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 medication. 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 medication 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.

If 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.

Contact one of the people on the Useful Contacts list overleaf if you want to discuss things further.

Top Tips from other parents

Best time
Think about when you can best fit the nebuliser into your everyday routine. 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 e.g. "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 a grown up. 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 medications 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. Give a 5-minute warning.

Distraction
Have other means of distraction handy as well as a DVD e.g. books and toys.

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 a tiny bit of medicine left over. You will know it is finished when the mist stops.

How do I wash the equipment?
Keeping your nebuliser clean is vitally important. Full written details will be given by your physiotherapist.

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

Senior Ward/Clinic Physiotherapist
Nicola Collins 0207 352 8121 Bleep 7304

Paediatric Pharmacy Team
Phone 0207 352 8121 ext 4375 or Bleeps 7425, 7410

Homecare Team – Physiotherapists
Emma Dixon 07970 269452
Nicky Murray 07791 584749

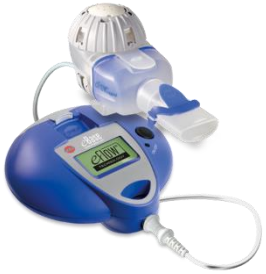
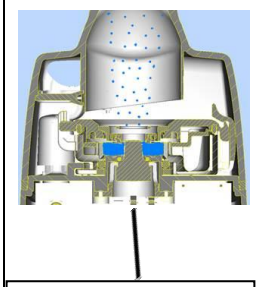
Homecare Team – Nursing
Katie Dick 07773 964573
Karen Henney 07971 224068
Caroline Devon 07483 338160
Laura Seddon 07973 173969

Appendix 9 - Physiotherapy adjunct & nebuliser device cleaning guide (for home)

Research suggests adjuncts and nebuliser devices that are not cleaned and left wet after use, can grow bacteria. It is therefore vitally important to prevent re-infection by **cleaning** the adjunct/device, **sterilising** it regularly and **air drying** it thoroughly. This document is to be used as a guide, your current adjunct and/or nebuliser device will have been provided by your physiotherapist after careful assessment and clinical reasoning.

Adjunct/Nebuliser	Cleaning	Sterilisation (use 1 method)	Replacements	Additional Notes
Infant PEP   *Pari PEP™ S, elbow bend, anaesthetic face mask*	Dismantle and wash all parts in hot soapy water, rinse, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. *if using an anaesthetic mask and green connector clean with an antibacterial wipe. Do not dismantle blue disc. **After every use**	• Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the length of cycle. Air dry after in a well ventilated space. **Daily**	Pari PEP: Should last a minimum of 12 months. Anaesthetic Mask: Replace when deflated or broken.	Store dismantled and put together for use only.
Bubble PEP 	**Tubing** Rinse tubing in hot soapy water, rinse, shake out excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. **Bottle** Empty water down the toilet. Rinse with hot water, shake out excess water and leave to air dry. **After every use**	*Soak bottle and tubing in Milton solution as per Milton guidelines. Air dry after in a well ventilated space. **Daily**	*Replace tubing and milk bottle every 2 weeks. One pack of tubing should be cut into 4. This should last 4 weeks.	Equipment: Suction tubing (approx. 80cm), 2 pint plastic milk bottle and washing up liquid. Where possible hang tubing vertically to dry thoroughly and alternate tubing so one is always dry.
Pari PEP™ S 	Dismantle and wash all parts in hot soapy water, rinse, vigorously shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. Do not dismantle blue disc. **After every use**	• Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the length of cycle. Air dry after in a well ventilated space. **Daily**	Should last a minimum of 12 months.	Store dismantled and put together for use only.

PEP/Rmt™ 	Dismantle and wash all parts in hot soapy water, rinse, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. *If using anaesthetic mask, clean with an antibacterial wipe. **After every use**	• Boil in water for 10 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the length of cycle. Air dry after in a well ventilated space. **Daily**	Should last a minimum of 1-3 years.	Store dismantled and put together for use only.
Acapella® Choice 	Dismantle and wash all parts in hot soapy water, rinse, vigorously shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. **After every use**	• Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Please note you can't steam sterilise an acapella choice® **Minimum of weekly – can be more**	Should last a minimum of 6 months. Can be purchased privately or via prescription from your GP. To order a new device, contact Henley Medical on 01707 333164. *Product code RTP277000 (£46.50).*	Store dismantled and put together for use only.
Pari OPEP® (or Flutter®) 	Dismantle and wash all parts in hot soapy water, rinse, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. **After every use**	• Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the length of cycle. Air dry after in a well ventilated space **Daily**	Should last a minimum of 12 months. Can be purchased privately. To order a new device, contact Pari Medical Ltd on 01932 341122. *Product Pari OPEP (£27.81 plus £3.50 P&P).*	Store dismantled and put together for use only.
Aerobika® 	Dismantle and wash all parts in hot soapy water (can leave to soak for 15 minutes), rinse, vigorously shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet.	• Boil in water for 5 minutes. Vigorously shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the length of cycle. Air dry after in a well ventilated space. • Soak in Milton	Should last a minimum of 12 months. Can be purchased privately. To order a new device, visit a Lloyds pharmacy. *Product code AER94A (£70-90 incl. VAT – VAT relief optional).*	Store dismantled and put together for use only.

	After every use	solution as per Milton guidelines. Air dry after in a well ventilated space. • Use a microwave steam bag can be used. Follow the manufacturer's instructions. **Daily**		
eFlow® 	Dismantle and wash all parts of the handset (including aerosol head/mesh) in hot soapy water, rinse, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. **After every use**	• Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the length of cycle. Air dry after in a well ventilated space. **Daily** <u>Once a week:</u> Use the Easycare system for the aerosol head/mesh, with either distilled water, deionised water or 0.9% saline.	<u>Handset:</u> Should last a minimum of 12 months. <u>Aerosol head/mesh:</u> Should last 3-6 months dependent on frequency of use.	Avoid touching the aerosol head/mesh. Use a separate handset and aerosol/mesh for inhaled antibiotics.
Philips Respironics I-neb 	Place mouthpiece, medication guide, drug chamber and chamber lid into the basket. Agitate in hot soapy water, rinse using cold boiled water, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. **After every use**	Boil the parts within the basket in water for 6-10 minutes with 1-2 drops of washing up liquid. Rinse using cold boiled water, shake off excess water and leave to air dry in a well ventilated space. **Weekly**	Chamber and mouthpiece should last up to 6 months. If on Promixin Contact Bionical on 0330 808 8668 Bionical.I-nhale@nhs.net for replacements.	Avoid touching the silver transducer horn.  Transducer
Pari LC® Sprint 	Dismantle and wash all parts in hot soapy water, rinse, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet.	• Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. • Use a steam steriliser and follow the manufacturers guidelines as to the	Should last a minimum of 12 months.	Do not wash compressor tubing. If moisture is present, attach the tubing to the compressor and run until droplets cannot be seen.

	After every use	length of cycle. Air dry after in a well ventilated space **Daily**		
Philips Respironics SideStream <u>Light Blue</u> (Reusable) <u>Dark Blue</u> (Disposable – not for home use) 	Dismantle and wash all parts in hot soapy water, rinse, shake off excess water and leave to air dry in a well ventilated space. Empty used water down the toilet. **After every use**	<u>Light Blue:</u> Boil in water for 5 minutes. Shake off excess water, leave to air dry in a well ventilated space. **Weekly** <u>Dark Blue:</u> Do not boil.	<u>Light Blue:</u> Replace every 6 months. <u>Dark Blue:</u> Can be used for up to 14 days only.	Do not wash compressor tubing. If moisture is present, attach the tubing to the compressor and run until droplets cannot be seen. Ensure mushroom shaped baffle is in place before using.

- Denotes no manufacturers guidelines – advice based on expert consensus

<u>Additional Information</u>

<u>Useful Hints</u>

- Tap out the residual nebulised medication after each use onto kitchen/toilet roll.
- Wash all adjuncts/nebuliser devices in a separate bowl/container (not in the sink). <u>Dispose of the water down the toilet and flush.</u>
- If using antibiotic filter pads, turn over after each nebulisation. Dispose at the end of the day after two uses.

<u>Compressor Servicing</u>

- Ensure your compressor is serviced annually, you will need to book an appointment in advance, this can be booked alongside any clinic appointment you may have.
- To book an appointment please contact the Outpatient Physiotherapy Department on 0207 351 8088.
    - (Opening hours 8.30am – 4.30pm).

New Parts and Questions

If you require a new adjunct or nebuliser parts, please contact the appropriate email/telephone number below.

- Child (CF) – Email NebPhysioEquipment@rbht.nhs.uk

UV Sterilising As a team we've been asked about UV light sterilisers to disinfect nebuliser and physiotherapy equipment.
We cannot recommend this type of steriliser due to the uncertainty of the UV light being able to reach all areas of the nebuliser or device and the impact it might have on the plastics.

Where possible these recommendations have been based on manufacturers advice/guidelines, where this has not been possible clinician consensus has been agreed between both adult and paediatric physiotherapy teams.

Appendix 10 – Sputum induction protocol

Indication for CF Sputum Induction:

Patients with CF (who are generally non-productive of sputum) with:

- Recurrent pulmonary exacerbations or declining lung function but no recent significant bacterial growth on cough swab sampling.
- Previous isolation of bacterial or fungal infection (including Non-Tuberculous Mycobacterium) - looking for additional growths to decide about treatment initiation or eradication success. (If post eradication perform sputum induction 2 weeks after stopping treatment).
- Previous growth of *Pseudomonas aeruginosa* (PA) to confirm eradication following treatment. (Sputum induction should be completed 2 weeks after stopping initial eradication treatment and 4 weeks after stopping long term antipseudomonal treatment).
- Previous growth of NTM with eradication treatment being commenced. Sputum induction should be completed quarterly during treatment and for 1 year after stopping treatment (4 samples required within the year).

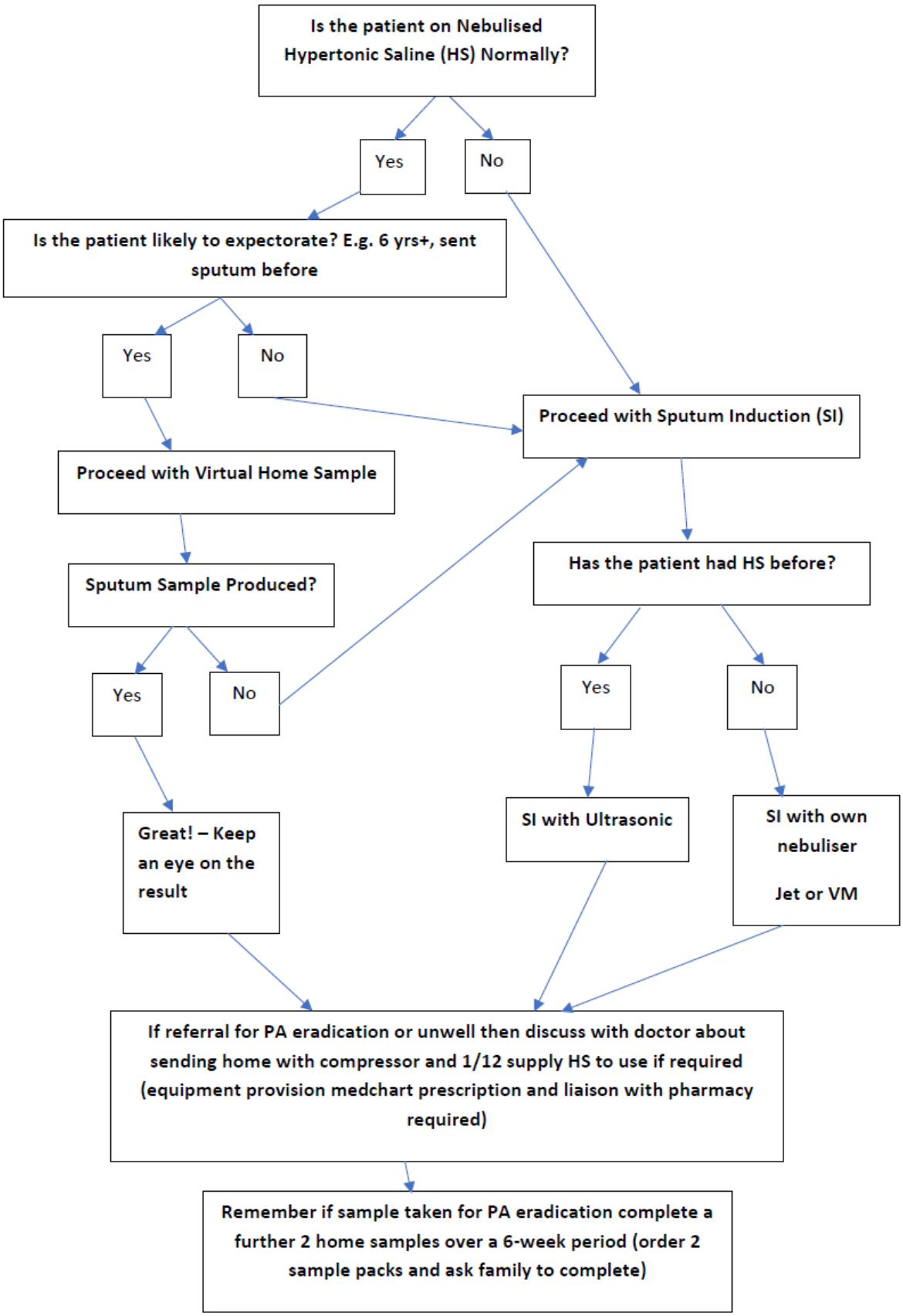
Inclusion Criteria:

- All patients with Cystic Fibrosis

Exclusion Criteria:

- COVID-19 PCR positive or COVID-19 screening positive
- Patients with a history of recent haemoptysis or pneumothorax
- Patients unwell on the day of the sputum induction e.g., diarrhoea, vomiting, temperature, increased work of breathing
- Patients with history of procedural distress around nebulised therapy (test to be carried out by physiotherapist with play and psychology involvement as appropriate)
- Patient referred to assess for bacterial eradication (e.g *Pseudomonas aeruginosa)* but still taking eradication/suppression treatment
- Patients with a history of bronchoconstriction to inhaled therapies should be discussed with the medical team before sputum induction is carried out as this may exclude them from the procedure.

Deciding between Hospital and Home Samples – Flow Diagram



Sputum Induction Protocol - In Hospital with Ultrasonic Nebuliser Device

Prior to the Procedure:

- The Referrer (doctor, nurse, physiotherapist) refers the patient via ICE or verbally with a completed form, stating the reason for referral and preferred timeframe of sputum induction.
- Phone or email the patient to arrange the appointment.
- Ask a medical or non-medical prescriber to complete **Sputum Induction Testing Patient Specific Direction** (Prescription) – See below. To include 36mls hypertonic saline (3 or 7%) and a pre- and post-inhaled bronchodilator (Salbutamol 100 micrograms MDI preferred unless previous allergy).
- COVID-19 pre-screening will be undertaken by a member of the physiotherapy team 24hrs prior to a visit. A COVID 19 triage questionnaire will be completed via telephone and uploaded to EPR. If patients report any COVID 19 symptoms, they will be told not to attend RB&HFT and given appropriate advice for further management of their symptoms. This should be documented on EPR.

During the Procedure:

- Collect and set up equipment for sputum induction and data collection sheet
- Ensure all medication is double checked and signed for by a registered healthcare practitioner (nurse/physiotherapist).
- A member of the physiotherapy team wearing appropriate PPE, will meet the patient. The patient (and parent/carer) will be escorted to the cubicle wearing appropriate PPE.
- As sputum induction is an aerosol generating procedure (AGP) it is carried out in the negative pressure cubicles in the CRF or individual room and staff must wear appropriate PPE
- Complete the sputum induction and record results on the data collection sheet.

Post Procedure:

- When an AGP has been undertaken it is recommended that the room is left vacant with the door closed for 30-60 minutes (depending on air exchanges) prior to performing a clean. The time starts when the AGP is completed and where applicable the patient has left the room. A relevant sign to be placed on each Cubicle door to alert other staff and service users, that an AGP has taken place, and when it's safe to re-enter the rooms without.
- Windows to the outside (where applicable) can be opened.
- If there is an infection risk as per Isolation Policy, contact ISS to undertake a terminal clean of the area, as per the Trust isolation policy
- If an AGP has taken place where there is no infection risk, please follow the SOP for cleaning post AGP (for no infection risks
- Upload completed sputum induction data collection sheet (Patient Specific Direction) to Electronic Patient Record/notes
- Complete trials spreadsheet and relevant sputum induction database
- RATAR (patient contact statistics)
- Chase result to inform referrer and patient of result
- Inform RBH CF team of result and plan of action

Please refer to the PPE table on the intranet for appropriate PPE

For paediatric induced sputa carried out in the CRF please also refer to: Clinical Research Facility (CRF) Local guidance on AGPs procedural tests conducted during COVID-19 and Guidance for management of Research Participant visits at Royal Brompton and Harefield Hospitals.

Sputum Induction Equipment Required

Nebuliser:

- Ultrasonic Nebuliser (DeVillbiss ultraneb nebuliser) & nebulising chamber with white transducer
- Disposable cup and lid for the nebuliser
- Elephant tubing (2 lengths: 1 and 4 sections)
- Bacterial Filter
- Mouthpiece/mask

Medication:

- Hypertonic saline 7% or 3% - 36mls (x9 vials)
- Salbutamol MDI 100mcg & Spacer
- 0.9% saline for flushing suction catheter

Spirometry and Assessment:

- Spirometer
- Calibration syringe
- Stethoscope
- Saturation monitor (with age-appropriate probe)
- Timer / Calculator (can use phone)

Suction: (Paediatrics only)

- Suction tubing and
- Size 10 suction catheter
- Green sputum trap x2

Microbiology:

- Sputum collection pot
- Cough swab x1
- Viral swab

For the patient:

- Drink of water
- Tissues
- Vomit bowl
- Own airway clearance device if relevant

Overview of the Procedure

- Assemble the ultrasonic nebuliser according to the manufacturer's instructions

  - Take a brief current history and note any oral antibiotics. Check the patient doesn't have any drug allergies or previous reactions to hypertonic saline or bronchodilator (in most cases this will be salbutamol).

  - If you don't need to know the patient's Bronchodilator Reversibility (this would be previously requested by the referrer) give patient a bronchodilator (usually 2 puffs Salbutamol or whatever dose they normally take pre- physio – refer to PSD) via MDI & spacer. Wait 15mins

  - Record the patient's height and weight for spirometry if appropriate

  - If age appropriate perform spirometry. From the best result of this spirometry calculate 10% and 20% drop in FEV_1 **use as safety value** for monitoring of the procedure. Fill in table on results page

  - Draw up 20 ml of 3% or 7 % hypertonic saline (as prescribed) and place in the ultrasonic nebuliser chamber.

  - Perform a cough swab (paediatrics only)

  - Perform baseline auscultation

  - Perform baseline oxygen saturation monitoring

  - Explain/demonstrate to the patient what they need to do and **Start first 5 min** period of nebulisation with hypertonic saline. Remember to set timer to 5 mins and to record time started.

  - **End of first 5 mins.** Ask the patient to rinse their mouth with water (if they can) and then to try and expectorate. For many patients' it is helpful to lean forward and perform 3 phases of sputum expectoration i.e.
    a) Huffing and coughing
    b) Clearing the throat, often noisily: "hawking"
    c) Spitting into the pot

  - Next - Take patient's spirometry (if age appropriate) prior to starting the next 5 min cycle of nebulisation. If <10% different to the baseline result continue with next 5-minute cycle of nebulisation (if >10% stop and see below). Perform auscultation and monitor oxygen saturations. Record all observations on the data collection sheet.

  - Top up the nebulising chamber with 8mls of hypertonic saline. Repeat the nebulisation for 2 more cycles of 5 minutes (15 minutes in total) – topping up with 8mls of hypertonic saline each time. Check SPO_2, auscultation and spirometry (if age

appropriate) at the end of each cycle. The FEV_1 must be within 10% of the initial baseline before proceeding and then leaving the department.

- At the end of the 15 minutes of nebulisation the patient should perform a few cycles of their normal airway clearance if appropriate or you may try graded huffs and or Autogenic Drainage and or exercise to achieve a good, expectorated sample.

- If the patient is unable to expectorate an adequate sputum sample oral suction should be performed with a size 10 catheter and sputum trap. We call this a "magic cough swab". The depth of suction is similar to a cough swab and is approximately the distance between patient's nostril and ear. The sample can be flushed into the trap using 0.9% saline. If possible try and remove suction while withdrawing the catheter back out the mouth (in practice this isn't always possible). With a child, a firm cuddle (by parent/carer) whilst supporting the child's forehead helps make this procedure quicker and more effective.

- Prior to the patient leaving the department you should let them know of any possible latent adverse reactions and what to do if they experience these

- If indicated (e.g., recurrent pulmonary exacerbations or declining lung function) split sputum sample in two and send one for bacteriology and the other for virology (respiratory PCR), or you may just do a viral swab for virology.

- All specimen pot(s) should be labelled with patient's name, date of birth, hospital number, date and time collected. Complete sample request (yellow form – bacteria, orange form virology or ICE request). All sputa to be sent for microscopy, culture and sensitivity (mc&s), AFB (acid fast bacilli) investigations and fungal culture. Cough Swab sent for mc&s.

STOP the sputum induction if:

The patient becomes wheezy
Develops chest discomfort
Oxygen saturations drop below 92% (>5% below baseline in patients with lower baseline saturations)
Has signs of increased work of breathing
$FEV_1 \geq$ 10% drop from baseline at any stage

They should be treated with bronchodilator as prescribed via large volume spacer.
Lung function should be repeated after 10-15 minutes.
If FEV_1 remains $\geq$ 10% drop from baseline, then discuss with medical team before continuing.

If Spirometry has returned to <10% difference to baseline and no other symptoms then continue with next nebulisation.

Should FEV_1 fall $\geq$ 20%, the induced sputum procedure must be stopped immediately, emergency bronchodilator to be given as prescribed and doctor called to review situation.
Repeat FEV_1 after 15 mins and medical team to review before discharged.

EMERGENCY PAEDIATRIC CONTACT NUMBERS AT RBH:

Please note - if you need medical attention during the trial there should be a paediatric nurse in the CRF, and a paediatric doctor in children's outpatients during the following times: Monday afternoon (CF), Tuesday morning (CLH resp), Wednesday afternoon (IBL/RP resp), Friday all day (except lunch time) – am CLH resp and pm CF.

Failing that please use the following numbers for advice:
Ex 82257 (non urgent advice)
78, Bleep 1448 (non urgent advice)
78, Bleep 1237 (urgent advice from the registrar on Rose Ward).
07971075601 (clinical lead physiotherapist paediatrics)
Bleep 7304 (ward physiotherapist)

CLEANING

- Disposable equipment should be thrown away.
- Reusable equipment - nebuliser chamber (not white transducer) should be cleaned by soaking in Tristel for 5 – 10 minutes (in lung function), rinsing in sterile water and left to air dry.
- White transducer should we wiped down using medical wipes e.g., Clinell.
- If there is an infection risk as per Isolation Policy, contact ISS to undertake a terminal clean of the area, as per the Trust isolation policy
- If an AGP has taken place where there is no infection risk, please follow the SOP for cleaning post AGP (for no infection risks)

Make sure to keep the transducer (base part of the ultrasonic nebuliser) – it is very expensive!

Make sure to keep the transducer (base part of the ultrasonic nebuliser) – it is very expensive!

SPUTUM INDUCTION TESTING PATIENT SPECFIC DIRECTION

*******THE TEST WILL NOT BE UNDERTAKEN WITHOUT ALL SHADED AREAS COMPLETED******

Terminal clean required post-test? *(i.e. MRSA/ M. abscessus/B. cepacia)*: **YES / NO**

HOSPITAL NUMBER **Wt** **kg** **SURNAME** **FIRST NAME** **D o B**	**Inpatient/ Outpatient**
DATE OF REFERRAL: **REASON FOR REFERRAL:** **PRESCRIBER: *PRINT*: .....** ***SIGN*.....** **PRESCRIBER BLEEP/ EXT no. #** **CONSULTANT:**	**ALLERGIES**

	Medicine	DOSE	Administered?	Initials for check
MEDICATION DOSE (36mls 7% or 3% hypertonic saline if using ultrasonic device)			**YES NO**	
PRE-TEST BRONCHODILATOR (salbutamol 100 micrograms MDI preferred unless previous allergy)			**YES NO**	
POST TEST OR DURING TEST BRONCHODILATOR Salbutamol nebuliser or Salbutamol 100 micrograms MDI (preferred unless previous allergy)			**YES NO**	

Sputum Induction Protocol Data Collection Sheet

Referral Information

Name of patient	
Date of Birth	
Hospital Number	

Sputum Induction requested by

Date of Referral		By when should Sputum Induction be done?	
Reason for referral			
Have they had sputum induction before?	**No / Yes** If Yes when? _____		
Any other Relevant Clinical Information?			

Assessment

Date of procedure			
Height:	**cm**	**Weight:**	**kg**
Pre sputum induction cough swab taken	**Tick to confirm completed:**		
Clinical presentation today	***Ask: Are you well today? Do you have any of the following (as appropriate): Cough/wheeze/ temperature/chest pain/coughing up blood/new breathlessness/increased work of breathing? Discuss with a senior physiotherapist, including todays spirometry if appropriate, before proceeding.***		

Current Antibiotics	**Oral:** **Nebulised:**
Check for Allergies	**Allergies?** **Yes/No** **If yes what?.....**
Inform Patient	**Possible Side Effects/Adverse Reactions: Increased heart rate, tremor, flushing, rash, swollen lips, tight chest, wheeze, difficulty breathing, drop in lung function, cough, sore throat, nausea** **Safety Net: Inform patient that any side effects/adverse reactions experienced should go before leaving the department, but they must inform you if they experience any delayed effects and if concerned go to their local hospitalTick to confirm completed:** **Verbal Consent for Sputum Induction (and administration of associated medications by registered or non-registered clinician) Obtained from Patient/Parent/Carer? (if non registered clinician make sure the patient/carer is aware of this)** **Tick to confirm completed:**

Sputum Induction Protocol Data Collection Sheet

Spirometry

Pre Bronchodilator **FEV_1 -** N/A unless want to check BDR (absolute and % pred)	FEV_1: FVC:
Post Bronchodilator **FEV_1** (absolute and % pred)	FEV_1: FVC:
Calculated FEV_1 10% drop : 0.9 x FEV_1 baseline (absolute)	FEV_1:
Calculated FEV_1 20 % drop 0.8 x FEV_1 baseline (absolute)	FEV_1:

Time started	Duration	Completed (Y/ N)	FEV_1/FVC/SpO2/ Auscultation	Sample produced (Y / N)	Comments
	Pre		SPO2 Ausc:		
	5 minutes		FEV_1 FVC SpO2 Ausc:		
	5 minutes		FEV_1 FVC SpO2 Ausc:		
	5 minutes		FEV_1 FVC SpO2 Ausc:		
	10 minutes post induction	If indicated The FEV_1 must be within 10% of the initial baseline before leaving the department.	FEV_1 FVC SpO2 Ausc:		
	Physio performed?		N/A		
	Oraopharyngeal Suction performed?		N/A		

Post Test or During Test Bronchodilator Administered: **Date given:**	Time given:	Dose given:	Initials for Check:
Post Test or During Test Bronchodilator Administered: **Date given:**	Time given:	Dose given:	Initials for Check:

Comments:

Signature: **Print Name:**

Job Title and Band: **Date:**

Sputum induction sample processing

Sample:	Send for:	Form:	Completed Y / N
INDUCED SPUTUM SAMPLE (expectorated or oropharyngeal suction)	MC&S, AFB FUNGAL	Yellow microbiology form	
OROPHARYNGEAL SUCTION SAMPLE OR VIRAL SWAB (if symptomatic)	VIROLOGY (Resp PCR)	Orange virology form	
COUGH SWAB (pre)	MC&S	Yellow microbiology form	

Appendix 11 – Sinus rinsing

A lifetime of specialist care

How to take a sinus rinse sample

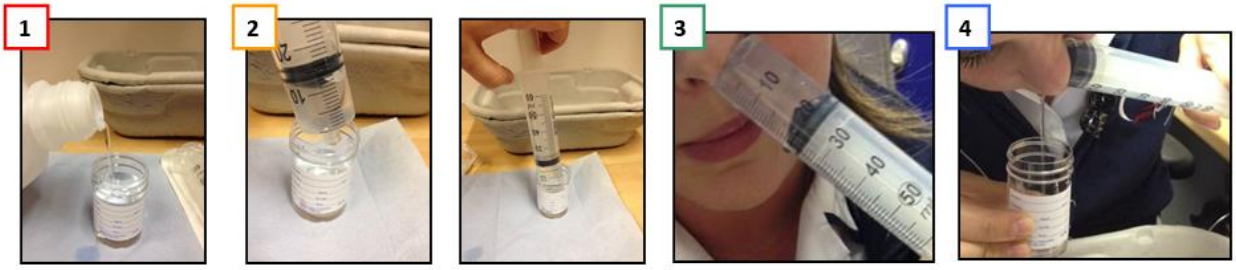
Royal Brompton & Harefield NHS
NHS Foundation Trust

Equipment required:

- 0.9% Saline (~50ml)
- 50ml Luer-lok syringe (short nozzle end)
- 1 silver lidded sample pot
- Disposable bowl
- Tissues

****IF TAKING A COUGH SWAB OR SPUTUM SAMPLE – PLEASE TAKE THIS BEFORE SINUS SAMPLE SO NOT CONTAMINATED****

1. On a flat surface, pour ~50ml of 0.9% saline into the sample pot
2. Syringe out the 0.9% saline into the 50ml syringe – turn upwards and void any air from the top of the syringe
3. Leaning over the bowl in sink/ on lap, place the syringe tightly against the nostril to ensure a good seal (warn the patient they may still be able to feel the nozzle of the syringe in their nose)
4. Place the sample pot under the other nostril (this may require a second pair of hands) to collect ~5-10mls of solution. When you have enough, encourage pt to gently blow out any residual fluid into the pot
5. Send off sample with yellow form labelled "nasal lavage" for MC&S
6. Allow patient to blow their nose and then dispose of bowl and fluid cleared into a yellow bin.



Nasal Douche/Nasal Rinse:

NeilMed SINUS RINSE™ is a squeeze bottle system that allows you to deliver saline solution with positive pressure to clean the nasal passages. In our experience it is worth trialling in symptomatic children from age 5 and upwards. The following information is taken from the NeilMed website and further details and instructional videos can be found there:
http://shopuk.neilmed.com/Products-UK/Sinus-Rinse-UK/Sinus-Rinse-Regular-Kit_4

Step 1

Step 1 Please wash your hands. Fill the clean bottle with the designated volume of lukewarm distilled, filtered or previously boiled water. You may warm the water in a microwave in increments of 5 to 10 seconds to avoid overheating the water, damaging the device or scalding your nasal passage.

Step 2

Step 2 Cut the SINUS RINSE™ mixture packet at the corner and pour its contents into the bottle. Tighten the cap and tube on the bottle securely. Place one finger over the tip of the cap and shake the bottle gently to dissolve the mixture.

Step 3

Step 3 Standing in front of a sink, bend forward to your comfort level and tilt your head down. Keeping your mouth open, without holding your breath (you may want to say "K"), place the cap snugly against your nasal passage. SQUEEZE BOTTLE GENTLY until the solution starts draining from the OPPOSITE nasal passage. Some may drain from your mouth. For a proper rinse, keep squeezing the bottle GENTLY until at least 1/4 to 1/2 (60 mL to 120 mL or 2 to 4 fl oz) of the bottle is used. Do not swallow the solution.

Step 4 Blow your nose very gently, without pinching nose completely to avoid pressure on eardrums. If tolerable, sniff in gently any residual solution remaining in the nasal passage once or twice because this may clean out the posterior nasopharyngeal area, which is the area at the back of your nasal passage. At times, some solution will reach the back of your throat, so please spit it out. To help drain any residual solution, blow your nose gently while tilting your head forward and to the opposite side of the nasal passage you just rinsed.

Step 5 Now repeat steps 3 and 4 for your other nasal passage.

Step 6 Clean the bottle and cap (see directions below). Air dry the SINUS RINSE™ bottle, cap, and tube on a clean paper towel or use NeilMed® NasaDOCK® or NasaDOCK® Plus (sold separately) to store the bottle, cap and tube.

It is very important to keep these devices clean and free from any contamination.
Replace the bottle every 3 months.

NeilMed® SINUS RINSE™ Squeeze Bottle: - Please perform routine inspections of the bottle and tube for any discolorations and cracks. If there are any visual signs of deterioration or permanent colour changes, please clean thoroughly. If the discolorations remain after cleansing, discard the items and purchase new ones. We strongly suggest that you follow all these steps after each use of the product.

- **Step 1:** Rinse the cap, tube and bottle using running water.
- **Step 2:** Add a few drops of dish washing liquid or baby shampoo.
- **Step 3:** Attach the cap and tube to the bottle; hold your finger over the opening in the cap and shake the bottle vigorously.
- **Step 4:** Squeeze the bottle hard to allow the soapy solution to clean the interior of the tube and the cap. Empty out the bottle completely.
- **Step 5:** Rinse the soap from the bottle, cap and tube thoroughly and place the items on a clean paper towel to dry or use the preferred NasaDOCK® or NasaDOCK Plus.

The NasaDOCK® is a simple, hygienic way to dry and store the SINUS RINSE™ bottle, cap and tube. NasaDOCK® comes with various hanging options and is available in different colours. Our newest model also offers storage for our SINUS RINSE™ mixture packets. We strongly suggest using NasaDOCK® as an inexpensive, easy way to dry the cap, tube and SINUS RINSE™ bottle.

- **Dishwasher Cleaning:** Do not use a dishwasher to clean the inside of a bottle. While our bottle is dishwasher safe, a dishwasher will not adequately clean the SINUS RINSE™ bottle. The water jets in dishwashers cannot enter the narrow neck of the bottle, and portions of the bottle's interior will not be cleaned thoroughly. Additional methods of cleaning the bottle include the use of concentrated white vinegar or isopropyl alcohol (70% concentration), followed by scrubbing and rinsing as described above.

Microwave Disinfection Clean the device with soap and water as mentioned above and shake off the excess water. Now place the bottle, cap and tube in the microwave for 40 seconds. This will disinfect the bottle, cap and tube. If the microwave has been used recently, please make sure that the inside of the microwave has cooled back down to room temperature before using it to disinfect the bottle.

Pari Sinus Nebuliser:

The Pari Sinus is a pulsating jet nebuliser. The added oscillations ensure the aerosol reaches the paranasal cavities. Dornase alfa, nebulised colistin or tobramycin may be given via the

Pari Sinus nebuliser, but this should be a consultant decision. We recommend **1 minute of nebuliser up each nostril** (**6x 10seconds** – tongue to back/top of mouth, hold breath and make 'k' sound to close the soft palate and help keep the neb going to the sinuses not the lungs), followed by completing the remaining medication via a mouthpiece to treat the lower airway. Due to the technique required for effective delivery we've found this easier in older children, and so wouldn't normally trial this until age 8 years and upwards. See patient information leaflet (Dornase alfa via Pari Sinus) below and visit https://www.pari.com/int/products/nose-and-nasal-sinuses/pari-sinus-int/ for further details.

With thanks to the RBH PCD team for the above information and patient information leaflet.

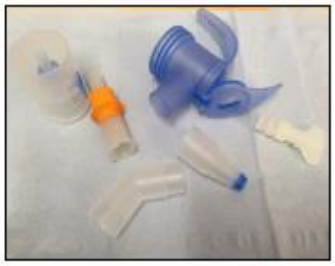
DNase (Pulmozyme) sinus neb

Once a day (when your nose is clearest) take your DNase nebuliser for your sinuses.



1. Remove the white bung and pour the DNase into the neb chamber & flip the blue lid down to close neb chamber
2. Ensure both tubes are attached to the neb (top and bottom) and the sinus nebuliser machine



3. Place the neb into one nostrils tightly and gentle squeeze (but don't block) your other nostril
4. Do **1 minute of neb up each nostril** (**6x 10seconds** – tongue to back/top of your mouth, hold your breath and make 'k' sound to close your soft palate and help keep the neb going to your sinuses not your lungs)
5. When you have completed treatment for each nostril, remove the nebuliser tube (labelled 'vibration' from the top of the neb pot) and **switch from the funnel for the nose to the mouthpiece or face mask**
6. Nebulise the rest of the DNase as you would your normal nebs.
7. Wash out neb parts and leave to air dry, sterilise once a week

TROUBLESHOOTING: If the vibrations from the nebuliser are causing a sensation of too much pressure/discomfort in your nose – remove the nebuliser tube (labelled 'vibration' from the machine end) and see if this helps. If there continues any further discomfort, please contact the Paeds Physio team.

Appendix 12 – NBS prompt sheet for Health Visitors contacting parents

Royal Brompton Hospital
Sydney Street
London
SW3 6NP

Children Cystic Fibrosis Newborn Screening Suggested Prompt Sheet

The following information outlines the Royal Brompton Hospitals (RBH) process for informing parents of a suspected Cystic Fibrosis result from the Newborn Screening (NBS) blood spot test and the rational.

Since October 2007 NBS for CF has been in place throughout the whole of the UK (1st July 2007 for those born in our region). When the screening labs contact RBH to inform us a patient's screen requires further investigations we start our NBS process for this child. We identify the child's health visiting team and contact them as a local resource as they know the child and family.

We ask Health Visiting (HV) teams to contact the parents to arrange a home visit and we have complied useful a prompt sheet below of what we hope will be said during this telephone call.

We have found that families really appreciated having a health visitor present at the appointment and value the time taken by both the HV and CNS to have a face to face meeting to talk through the process of CF suspected. It is beneficial for the both the family and RBH team as we are often building a lifelong relationship between specialist centre and the family.

The pathway the CF team at Royal Brompton follows is:

- RBHT informed of NBS results from the laboratory Monday though to Friday
- RBHT contacts HV (See prompt sheet below) and asks them to call parents on the morning (9am) of Monday or Wednesday (whichever is the next day) make an appointment with a nurse and asking for the other parent/relative to also be present. HV also to update the CNS team if there are any safeguarding/social concerns.
- CNS visits home accompanied by HV to inform parents that a diagnosis of CF is suspected.
- CNS arranges for a Sweat test to be undertaken the next day at RBHT on a Tuesday or Thursday
- Parents visit RBHT for sweat test and depending on results will meet with CNS and Consultant to discuss diagnosis
- Parent and patient attend RBH for 2 day NBS education where they meet the MDT one week after the sweat test

Suggested Telephone Script

We realise this is a difficult call for you the health visitor to make and we really appreciate your support. If you have questions regarding the information please do not hesitate in contacting the Children's CF nursing Team on the details below:

- Paediatric CF Nursing Team
- Telephone: 0207 351 8755
- Email: PaediatricCFCNSTeam@rbht.nhs.uk

Telephone script for the HV to follow when calling the parents

Script	Rationale
Please telephone parent on Mon (or Wed) whichever was advised at 9.00a.m (if no answer, please try again rather than leave a message in the first instance, however, if after a couple of tries still no answer, then you may have to leave a message requesting a call back – ideally to your work mobile number so that you are prepared for the call)	We ask to call at 9 as this should give them enough time to call Baby X's father/mother or close relative to be at home with them for the visit. We do not call ourselves as we have had no interaction with the family yet and feel the HV are a service already known to the child. We do not wish to get drawn into breaking the bad news over the phone if we state who we are and the intention of the call. We would not know where the person is at the time of the call or if they are supported or not.
Introduce yourself, name and designation and state you are the Baby X local HV	We know families never forget the moment this news of CF suspected is broken to them. This is why we want local professional support present with the CNS to answer questions with expertise and confidence. Both HV and CNS will be heavily involved with these families in the initial years and our parents have stated they really appreciate the involvement right from the start
The purpose of this call today is to let you know that we have been informed about the results of Baby X's heel spot test and myself and a nurse would like to meet you and discuss the results.	We ask you not to say which hospital we are from as if the family Google Newborn blood spot and Royal Brompton Hospital, the page from the CF guidelines is one of the top results. We do not want families to find this information out when they do not have the support of specialist nurses with them. **If parents ask for more information we recommend saying 'The nurse who contacted me this morning wants to talk to you in person rather than over the phone so they can give you dedicated time and information, please can we make the appointment and talk then' **If pushed further, please use your judgement to decide if you should share more information being mindful this may increase anxiety further without you knowing who is at home to support the parent and a lack of specialist information.
We think it would be good if you could arrange for your husband or partner (ideally) or a friend or family member to be there too. We are mindful that they may already have left for work and that is why we will come later this a.m. or p.m. to give them time to return	We ask for a friend/family member to be with them, as this can be difficult meeting and we know it would be very hard for the mother to relay the information to the dad after we have left the home. We understand this makes the appointment sound very ominous, but families have told us how appreciative they are that both parents were present.
Thank you. We will see you at X O'clock. Goodbye	
We ask that the HV then calls the CNS who made the call in order that the visit may be confirmed.	

Additional information: **Clinical Guidelines: Care of Children with Cystic Fibrosis Royal Brompton Hospital**
Page 43 Newborn Screening http://www.rbht.nhs.uk/childrencf/

Appendix 13 – Gene variants' nomenclature

More details are available from CFTR2 database. www.cftr2.org. Table adapted from CFTR2 database ©Copyright 2011 US CF Foundation, Johns Hopkins University, The Hospital for Sick Children. As of the most recent file (29 April 2022), a total of 485 variants are annotated on the CFTR2 website: CF-causing: 401; Variants of varying clinical consequence: 49; Non CF-causing: 24;Variants of unknown significance: 11.

Variant cDNA name (ordered 5' to 3')	Variant protein name	Variant legacy name	Variant final determination 29 April 2022 (current version)
c.(?_-1270)_(53+1_54-1)del	No protein name	CFTRdelePr-1	CF-causing
c.-9_14del23	No protein name	124del23bp	CF-causing
c.-8G>C	No protein name	125G/C	Non CF-causing
c.(?_1)_(53+1_54-1)del	p.Glu2GlyfsX17	CFTRdele1	CF-causing
c.1A>G	p.Met1Val	M1V	CF-causing
c.4C>T	p.Gln2X	Q2X	CF-causing
c.[4C>T;7A>T]	p.[Gln2X;Arg3Trp]	Q2X;R3W	CF-causing
c.11C>A	p.Ser4X	S4X	CF-causing
c.14C>T	p.Pro5Leu	P5L	Varying clinical consequence
c.38C>T	p.Ser13Phe	S13F	CF-causing
c.44T>C	p.Leu15Pro	L15P	CF-causing
c.50delT	p.Phe17SerfsX8	182delT	CF-causing
c.50dupT	p.Ser18GlnfsX27	175insT	CF-causing
c.(53+1_54-1)_(164+1_165-1)del	No protein name	CFTRdele2	CF-causing
c.(53+1_54-1)_(489+1_490-1)del	No protein name	CFTRdele2-4	CF-causing
c.53+1G>T	No protein name	185+1G->T	CF-causing
c.54-5940_273+10250del21kb	p.Ser18ArgfsX16	CFTRdele2,3	CF-causing

c.54-5842_489+401del	No protein name	IVSI-5842_IVS4+401del	CF-causing
c.57G>A	p.Trp19X	W19X	CF-causing
c.79G>A	p.Gly27Arg	G27R	CF-causing
c.79G>T	p.Gly27X	G27X	CF-causing
c.88C>T	p.Gln30X	Q30X	CF-causing
c.91C>T	p.Arg31Cys	R31C	Non CF-causing
c.92G>T	p.Arg31Leu	R31L	Unknown significance
c.115C>T	p.Gln39X	Q39X	CF-causing
c.137C>A	p.Ala46Asp	A46D	CF-causing
c.164+1G>A	No protein name	296+1G->A	CF-causing
c.164+1G>T	No protein name	296+1G->T	CF-causing
c.(164+1_165-1)_(1584_+1_1585-1)del(2619+1_2620-1)_(2988+1_2989-1)del	No protein name	CFTRdele3-10,14b-16	CF-causing
c.164+28A>G	No protein name	296+28A->G	Unknown significance
c.164+2T>C	No protein name	296+2T->C	CF-causing
c.164+4dupT	No protein name	296+3insT	CF-causing
c.165-3C>T	No protein name	297-3C->T	Unknown significance
c.165-1G>A	No protein name	297-1G->A	CF-causing
c.166G>A	p.Glu56Lys	E56K	CF-causing
c.168delA	p.Glu56AspfsX35	300delA	CF-causing
c.169T>G	p.Trp57Gly	W57G	CF-causing
c.170G>A or c.171G>A	p.Trp57X	W57X	CF-causing
c.175dupA	p.Arg59LysfsX10	306insA	CF-causing
c.174_177delTAGA	p.Asp58GlufsX32	306delTAGA	CF-causing
c.178G>A	p.Glu60Lys	E60K	CF-causing
c.178G>T	p.Glu60X	E60X	CF-causing
c.200C>T	p.Pro67Leu	P67L	CF-causing
c.202A>T	p.Lys68X	K68X	CF-causing
c.220C>T	p.Arg74Trp	R74W	Varying clinical consequence
c.223C>T	p.Arg75X	R75X	CF-causing

c.224G>A	p.Arg75Gln	R75Q	Non CF-causing
c.233dupT	p.Trp79LeufsX32	365-366insT	CF-causing
c.254G>A	p.Gly85Glu	G85E	CF-causing
c.262_263delTT	p.Leu88IlefsX22	394delTT	CF-causing
c.263T>A or c.263T>G	p.Leu88X	L88X	CF-causing
c.271G>A	p.Gly91Arg	G91R	CF-causing
c.(273+1_274-1)_(1116+1_1117-1)del	No protein name	CFTRdele4-7	CF-causing
c.(273+1_274-1)_(1584+1_1585-1)del	No protein name	CFTRdele4-10	CF-causing
c.(273+1_274-1)_(1679+1_1680-1)del	No protein name	CFTRdele4-11	CF-causing
c.(273+1_274-1)_(1116+1_1117-1)del(1584+1_1585-1)_(3468+1_3469-1)del	No protein name	CFTR50kbdel	CF-causing
c.273+1G>A	No protein name	405+1G->A	CF-causing
c.273+3A>C	No protein name	405+3A->C	CF-causing
c.274-2A>G	No protein name	406-2A->G	CF-causing
c.274-1G>A	No protein name	406-1G->A	CF-causing
c.274G>A	p.Glu92Lys	E92K	CF-causing
c.274G>T	p.Glu92X	E92X	CF-causing
c.292C>T	p.Gln98X	Q98X	CF-causing
c.293A>G	p.Gln98Arg	Q98R	CF-causing
c.296C>T	p.Pro99Leu	P99L	CF-causing
c.305T>G	p.Leu102Arg	L102R	CF-causing
c.310delA	p.Arg104GlufsX3	442delA	CF-causing
c.313delA	p.Ile105SerfsX2	444delA	CF-causing
c.325_327delTATinsG	p.Tyr109GlyfsX4	457TAT->G	CF-causing
c.327T>A	p.Tyr109X	Y109X	CF-causing
c.328G>C	p.Asp110His	D110H	CF-causing
c.330C>A	p.Asp110Glu	D110E	Varying clinical consequence
c.346G>A	p.Glu116Lys	E116K	CF-causing
c.349C>T	p.Arg117Cys	R117C	CF-causing

c.349C>G	p.Arg117Gly	R117G	Varying clinical consequence
c.350G>A	p.Arg117His	R117H	Varying clinical consequence
c.350G>C	p.Arg117Pro	R117P	CF-causing
c.350G>T	p.Arg117Leu	R117L	Varying clinical consequence
c.[350G>A;1210−12T[5]]	p[.Arg117His;No protein name]	R117H;5T	CF-causing
c.[350G>A;1210−12T[7]]	p.[Arg117His;No protein name]	R117H;7T	Varying clinical consequence
c.358G>A	p.Ala120Thr	A120T	Varying clinical consequence
c.366T>A	p.Tyr122X	Y122X	CF-causing
c.377G>A	p.Gly126D	G126D	CF-causing
c.409delC	p.Leu137SerfsX16	541delC	CF-causing
c.413_415dupTAC	p.Leu138dup	L138ins	CF-causing
c.416A>G	p.His139Arg	H139R	CF-causing
c.424delA	p.Ile142PhefsX11	556delA	CF-causing
c.429delT	p.Phe143LeufsX10	557delT	CF-causing
c.442delA	p.Ile148LeufsX5	574delA	CF-causing
c.443T>C	p.Ile148Thr	I148T	Non CF-causing
c.470_483delTTAGTTTGATTTAT	p.Phe157X	602del14	CF-causing
c.481T>G	p.Tyr161Asp	Y161D	CF-causing
c.489+1G>T	No protein name	621+1G->T	CF-causing
c.489+3A>G	No protein name	621+3A->G	Varying clinical consequence
c.494T>C	p.Leu165Ser	L165S	CF-causing
c.509G>A	p.Arg170His	R170H	Non CF-causing
c.531delT	p.Ile177MetfsX12	663delT	CF-causing
c.531dupT	p.Gly178TrpfsX5	663insT	CF-causing

c.532G>A	p.Gly178Arg	G178R	CF-causing
c.543_546delTAGT	p.Leu183PhefsX5	675del4	CF-causing
c.571T>G	p.Phe191Val	F191V	CF-causing
c.575A>G	p.Asp192Gly	D192G	CF-causing
c.577G>A	p.Glu193Lys	E193K	CF-causing
c.577G>T	p.Glu193X	E193X	CF-causing
c.579+1G>T	No protein name	711+1G->T	CF-causing
c.579+3A>G	No protein name	711+3A->G	CF-causing
c.579+5G>A	No protein name	711+5G->A	CF-causing
c.580-2A>G	No protein name	712-2A->G	CF-causing
c.580-1G>T	No protein name	712-1G->T	CF-causing
c.580G>A	p.Gly194Arg	G194R	CF-causing
c.580G>T	p.Gly194X	G194X	CF-causing
c.581G>T	p.Gly194Val	G194V	Varying clinical consequence
c.595C>T	p.His199Tyr	H199Y	CF-causing
c.601G>A	p.Val201Met	V201M	Unknown significance
c.613C>T	p.Pro205Ser	P205S	CF-causing
c.617T>G	p.Leu206Trp	L206W	CF-causing
c.647G>A	p.Trp216X	W216X	CF-causing
c.653T>A	p.Leu218X	L218X	CF-causing
c.658C>T	p.Gln220X	Q220X	CF-causing
c.675T>A	p.Cys225X	C225X	CF-causing
c.680T>G	p.Leu227Arg	L227R	CF-causing
c.695T>A	p.Val232Asp	V232D	CF-causing
c.709C>G	p.Gln237Glu	Q237E	Varying clinical consequence
c.717delG	p.Leu240X	849delG	CF-causing
c.722_743delGGAGAATGATGATGAAGTACAG	p.Gly241GlufsX13	852del22	CF-causing
c.(743+1_744-1)_(1584+1_1585-1)dup	No protein name	CFTRdup6b-10	CF-causing
c.744-2A>G	No protein name	876-2A->G	CF-causing

c.761delA	p.Lys254ArgfsX7	892delA	CF-causing
c.772A>G	p.Arg258Gly	R258G	Varying clinical consequence
c.794T>G	p.Met265Arg	M265R	Varying clinical consequence
c.803delA	p.Asn268IlefsX17	935delA	CF-causing
c.825C>G	p.Tyr275X	Y275X	CF-causing
c.828C>A	p.Cys276X	C276X	CF-causing
c.850dupA	p.Met284AsnfsX3	977insA	CF-causing
c.861_865delCTTAA	p.Asn287LysfsX19	991del5	CF-causing
c.868C>T	p.Gln290X	Q290X	CF-causing
c.933C>G or c.933C>A	p.Phe311Leu	F311L	CF-causing
c.935_937delTCT	p.Phe312del	F312del	Varying clinical consequence
c.941G>A	p.Gly314Glu	G314E	Varying clinical consequence
c.948delT	p.Phe316LeufsX12	1078delT	CF-causing
c.958T>G	p.Leu320Val	L320V	Non CF-causing
c.987delA	p.Gly330GlufsX39	1119delA	CF-causing
c.988G>T	p.Gly330X	G330X	CF-causing
c.1000C>T	p.Arg334Trp	R334W	CF-causing
c.1001G>A	p.Arg334Gln	R334Q	Varying clinical consequence
c.1001G>T	p.Arg334Leu	R334L	CF-causing
c.1006_1007insG	p.Ile336SerfsX28	1138insG	CF-causing
c.1007T>A	p.Ile336Lys	I336K	CF-causing
c.1013C>T	p.Thr338Ile	T338I	CF-causing
c.1021T>C	p.Ser341Pro	S341P	CF-causing
c.1021_1022dupTC	p.Phe342HisfsX28	1154insTC	CF-causing
c.1029delC	p.Cys343X	1161delC	CF-causing
c.1037T>C	p.Leu346Pro	L346P	CF-causing

c.1040G>A	p.Arg347His	R347H	CF-causing
c.1040G>C	p.Arg347Pro	R347P	CF-causing
c.1046C>T	p.Ala349Val	A349V	Unknown significance
c.1054C>T	p.Arg352Trp	R352W	Varying clinical consequence
c.1055G>A	p.Arg352Gln	R352Q	CF-causing
c.1057C>T	p.Gln353X	Q353X	CF-causing
c.[1075C>A;1079C>A]	p.[Gln359Lys;Thr360Lys]	Q359K/T360K	CF-causing
c.1076A>G	p.Gln359Arg	Q359R	Varying clinical consequence
c.1081delT	p.Trp361GlyfsX8	1213delT	CF-causing
c.1116+1G>A	No protein name	1248+1G->A	CF-causing
c.1117-1G>A	No protein name	1249-1G->A	CF-causing
c.1130dupA	p.Gln378AlafsX4	1259insA	CF-causing
c.1135G>T	p.Glu379X	E379X	CF-causing
c.1155_1156dupTA	p.Asn386IlefsX3	1288insTA	CF-causing
c.1202G>A or c.1203G>A	p.Trp401X	W401X	CF-causing
c.1209+1G>A	No protein name	1341+1G->A	CF-causing
c.1210−12T[5]	No protein name	5T	Varying clinical consequence
c.1210-33_1210-6GT[11]T[4]	No protein name	5T;TG11	Non CF-causing
c.1210-33_1210-6GT[12]T[4]	No protein name	5T;TG12	Varying clinical consequence
c.1210-33_1210-6GT[13]T[4]	No protein name	5T;TG13	Varying clinical consequence
c.1210−12T[7]	No protein name	7T	Non CF-causing
c.1210−12T[9]	No protein name	9T	Non CF-causing
c.1210-2A>C	No protein name	1342-2A->C	CF-causing
c.1211delG	p.Gly404AspfsX38	1343delG	CF-causing
c.1240C>T	p.Gln414X	Q414X	CF-causing
c.1301C>A or c.1301C>G	p.Ser434X	S434X	CF-causing

c.1301_1307delCACTTCT	p.Ser434LeufsX6	1429del7	CF-causing
c.1327G>T	p.Asp443Tyr	D443Y	Varying clinical consequence
c.1327_1330dupGATA	p.Ile444ArgfsX3	1461ins4	CF-causing
c.1330_1331delAT	p.Ile444X	1460delAT	CF-causing
c.1340delA	p.Lys447ArgfsX2	1471delA	CF-causing
c.1358T>C	p.Leu453Ser	L453S	CF-causing
c.1364C>A	p.Ala455Glu	A455E	CF-causing
c.1365_1366delGG	p.Val456CysfsX25	1497delGG	CF-causing
c.1367T>C	p.Val456Ala	V456A	CF-causing
c.1373delG	p.Gly458AspfsX11	1504delG	CF-causing
c.(1392+1_1393-1)_(1584+1_1585-1)del	No protein name	CFTRdele10	CF-causing
c.1393-1G>A	No protein name	1525-1G->A	CF-causing
c.1393-2A>G	No protein name	1525-2A->G	CF-causing
c.1397C>A or c.1397C>G	p.Ser466X	S466X	CF-causing
c.[1397C>G;3209G>A]	p.[Ser466X;Arg1070Gln]	S466X;R1070Q	CF-causing
c.1400T>C	p.Leu467Pro	L467P	CF-causing
c.1408A>G	p.Met470Val	M470V	Non CF-causing
c.1418delG	p.Gly473GlufsX54	1548delG	CF-causing
c.1420G>A	p.Glu474Lys	E474K	CF-causing
c.1466C>A	p.Ser489X	S489X	CF-causing
c.1475C>T	p.Ser492Phe	S492F	CF-causing
c.1477_1478delCA	p.Gln493ValfsX10	1609delCA	CF-causing
c.1477C>T	p.Gln493X	Q493X	CF-causing
c.1487G>A	p.Trp496X	W496X	CF-causing
c.1505T>C	p.Ile502Thr	I502T	CF-causing
c.1519_1521delATC	p.Ile507del	I507del	CF-causing
c.1521_1523delCTT	p.Phe508del	F508del	CF-causing
c.[1521_1523delCTT;3080T>C]	p.[Phe508del;Ile1027Thr]	F508del;I1027T	CF-causing
c.1523T>G	p.Phe508Cys	F508C	Non CF-causing
c.[1523T>G;3752G>A]	p.[Phe508Cys;Ser1251Asn]	F508C;S1251N	CF-causing

c.1538A>G	p.Asp513Gly	D513G	CF-causing
c.1545_1546delTA	p.Tyr515X	1677delTA	CF-causing
c.1558G>T	p.Val520Phe	V520F	CF-causing
c.1572C>A	p.Cys524X	C524X	CF-causing
c.1573C>T	p.Gln525X	Q525X	CF-causing
c.1584G>A	p.Glu528Glu	1716G/A	Non CF-causing
c.1584+1G>A	No protein name	1716+1G->A	CF-causing
c.(1584+1_1585-1)_(1679+1_1680-1)del	No protein name	CFTRdele11	CF-causing
c.1585-2A>G	No protein name	1717-2A->G	CF-causing
c.1585-1G>A	No protein name	1717-1G->A	CF-causing
c.1585-8G>A	No protein name	1717-8G->A	CF-causing
c.1624G>T	p.Gly542X	G542X	CF-causing
c.1645A>C or c.1647T>G or c.1647T>A	p.Ser549Arg	S549R	CF-causing
c.1646G>A	p.Ser549Asn	S549N	CF-causing
c.1648G>T	p.Gly550X	G550X	CF-causing
c.1650delA	p.Gly551ValfsX8	1782delA	CF-causing
c.1651G>A	p.Gly551Ser	G551S	CF-causing
c.1652G>A	p.Gly551Asp	G551D	CF-causing
c.1654C>T	p.Gln552X	Q552X	CF-causing
c.1657C>T	p.Arg553X	R553X	CF-causing
c.1670delC	p.Ser557PhefsX2	1802delC	CF-causing
c.1673T>C	p.Leu558Ser	L558S	CF-causing
c.1675G>A	p.Ala559Thr	A559T	CF-causing
c.1679+1G>C	No protein name	1811+1G->C	CF-causing
c.1679G>A	p.Arg560Lys	R560K	CF-causing
c.1679G>C	p.Arg560Thr	R560T	CF-causing
c.1679+1G>A	No protein name	1811+1G->A	CF-causing
c.1680-886A>G	No protein name	1811+1634A->G or 1811+1.6kbA->G	CF-causing
c.1680-877G>T	No protein name	1811+1643G->T	CF-causing
c.1680-1G>A	No protein name	1812-1G->A	CF-causing

c.1680A>C	p.Arg560Ser	R560S	CF-causing
c.1682C>A	p.Ala561Glu	A561E	CF-causing
c.1684G>A	p.Val562Ile	V562I	Non CF-causing
c.1687T>A	p.Tyr563Asn	Y563N	CF-causing
c.1687T>G	p.Tyr563Asp	Y563D	CF-causing
c.1689C>A	p.Tyr563X	Y563X	CF-causing
c.1692delA	p.Asp565MetfsX7	1824delA	CF-causing
c.1703delT	p.Leu568CysfsX4	1833delT	CF-causing
c.1705T>G	p.Tyr569Asp	Y569D	CF-causing
c.1721C>A	p.Pro574His	P574H	CF-causing
c.1724T>A	p.Phe575Tyr	F575Y	Varying clinical consequence
c.1727G>C	p.Gly576Ala	G576A	Non CF-causing
c.1731C>A	p.Tyr577X	Y577X	CF-causing
c.1736A>G	p.Asp579Gly	D579G	Varying clinical consequence
c.1753G>T	p.Glu585X	E585X	CF-causing
c.1763A>T	p.Glu588Val	E588V	Varying clinical consequence
c.1766+1G>A	No protein name	1898+1G->A	CF-causing
c.1766+1G>C	No protein name	1898+1G->C	CF-causing
c.1766+1G>T	No protein name	1898+1G->T	CF-causing
c.(1766+1_1767-1)_(2619+1_2620-1)del	No protein name	CFTRdele13,14a	CF-causing
c.1766+2T>A	No protein name	1898+2T->A	CF-causing
c.1766+3A>G	No protein name	1898+3A->G	CF-causing
c.1766+5G>T	No protein name	1898+5G->T	CF-causing
c.1792_1798delAAAACTA	p.Lys598GlyfsX11	1924del7	CF-causing
c.1801A>T	p.Ile601Phe	I601F	CF-causing
c.1820_1903del84	p.Met607_Gln634del	1949del84	CF-causing
c.1826A>G	p.His609Arg	H609R	CF-causing
c.1837G>A	p.Ala613Thr	A613T	CF-causing

c.1841A>G	p.Asp614Gly	D614G	Varying clinical consequence
c.1853T>C	p.Ile618Thr	I618T	Varying clinical consequence
c.1865G>A	p.Gly622Asp	G622D	Varying clinical consequence
c.1882G>C or c.1882G>A	p.Gly628Arg	G628R	CF-causing
c.1911delG	p.Gln637HisfsX26	2043delG	CF-causing
c.1920_1921dupTA	p.Ser641IlefsX23	2053insTA	CF-causing
c.1923_1931delinsA	p.Ser641ArgfsX5	2055del9->A	CF-causing
c.1943delA	p.Asp648ValfsX15	2075delA	CF-causing
c.1966G>T	p.Glu656X	E656X	CF-causing
c.1973_1985del13insAGAAA	p.Arg658LysfsX4	2105-2117del13insAGAAA	CF-causing
c.1986_1989delAACT	p.Thr663ArgfsX8	2118del4	CF-causing
c.1990G>T	p.Glu664X	E664X	CF-causing
c.2002C>T	p.Arg668Cys	R668C	Non CF-causing
c.2012delT	p.Leu671X	2143delT	CF-causing
c.2017G>T	p.Gly673X	G673X	CF-causing
c.2051_2052delAAinsG	p.Lys684SerfsX38	2183AA->G	CF-causing
c.2052dupA	p.Gln685ThrfsX4	2184insA	CF-causing
c.2052delA	p.Lys684AsnfsX38	2184delA	CF-causing
c.2053dupC	p.Gln685ProfsX84	2185insC	CF-causing
c.2053C>T	p.Gln685X	Q685X	CF-causing
c.2125C>T	p.Arg709X	R709X	CF-causing
c.2128A>T	p.Lys710X	K710X	CF-causing
c.2143C>T	p.Gln715X	Q715X	CF-causing
c.2158C>T	p.Gln720X	Q720X	CF-causing
c.2175dupA	p.Glu726ArgfsX4	2307insA	CF-causing
c.2195T>G	p.Leu732X	L732X	CF-causing
c.2215delG	p.Val739TyrfsX16	2347delG	CF-causing

c.2233G>T	p.Gly745X	G745X	CF-causing
c.2241_2248delGATACTGC	p.Ile748SerfsX28	2372del8	CF-causing
c.2249C>T	p.Pro750Leu	P750L	Varying clinical consequence
c.2260G>A	p.Val754Met	V754M	Non CF-causing
c.2290C>T	p.Arg764X	R764X	CF-causing
c.2353C>T	p.Arg785X	R785X	CF-causing
c.2374C>T	p.Arg792X	R792X	CF-causing
c.2421A>G	p.Ile807Met	I807M	Non CF-causing
c.2423_2424dupAT	p.Ser809IlefsX13	2556insAT	CF-causing
c.2453delT	p.Leu818TrpfsX3	2585delT	CF-causing
c.2463_2464delTG	p.Ser821ArgfsX4	2594delGT	CF-causing
c.2464G>T	p.Glu822X	E822X	CF-causing
c.2490+1G>A	No protein name	2622+1G->A	CF-causing
c.2491G>T	p.Glu831X	E831X	CF-causing
c.2502dupT	p.Asp835X	2634insT	CF-causing
c.2506G>T	p.Asp836Tyr	D836Y	Non CF-causing
c.2537G>A or c.2538G>A	p.Trp846X	W846X	CF-causing
c.2547C>A	p.Tyr849X	Y849X	CF-causing
c.2551C>T	p.Arg851X	R851X	CF-causing
c.2562T>C or c.2562T>G or c.2562T>A	p.Thr854Thr	T854T	Non CF-causing
c.2583delT	p.Phe861LeufsX3	2711delT	CF-causing
c.2589_2599delAATTTGGTGCT	p.Ile864SerfsX28	2721del11	CF-causing
c.2601dupA	p.Val868SerfsX28	2732insA	CF-causing
c.(2619+1_2620-1)_(3367+1_3368-1)del	No protein name	CFTRdele14b-17b	CF-causing
c.2620-26A>G	No protein name	2752-26A->G	Unknown significance
c.2645G>A	p.Trp882X	W882X	CF-causing
c.2657+2_2657+3insA	No protein name	2789+2insA	Unknown significance
c.2657+5G>A	No protein name	2789+5G->A	CF-causing
c.2658-1G>C	No protein name	2790-1G->C	CF-causing
c.2668C>T	p.Gln890X	Q890X	CF-causing

c.2735C>A	p.Ser912X	S912X	CF-causing
c.2735C>T	p.Ser912Leu	S912L	Unknown significance
c.2737_2738insG	p.Tyr913X	2869insG	CF-causing
c.2739T>A	p.Tyr913X	Y913X	CF-causing
c.2763_2764dupAG	p.Val922GlufsX2	2896insAG	CF-causing
c.2770G>A	p.Asp924Asn	D924N	Unknown significance
c.2780T>C	p.Leu927Pro	L927P	CF-causing
c.2797A>G	p.Arg933Gly	R933G	Varying clinical consequence
c.2810dupT	p.Val938GlyfsX37	2942insT	CF-causing
c.2822delT	p.Leu941GlnfsX27	2954delT	CF-causing
c.2825delT	p.Ile942ThrfsX26	2957delT	CF-causing
c.2834C>T	p.Ser945Leu	S945L	CF-causing
c.2855T>C	p.Met952Thr	M952T	Unknown significance
c.2859_2890delACATTCTGTTCTTCAAGCACCTATGTCAACCC	p.Leu953PhefsX11	2991del32	CF-causing
c.2875delG	p.Ala959HisfsX9	3007delG	CF-causing
c.2896delA	p.Thr966ArgfsX2	3028delA	CF-causing
c.2900T>C	p.Leu967Ser	L967S	Varying clinical consequence
c.2908G>C	p.Gly970Arg	G970R	CF-causing
c.(2908+1_2909-1)_(3367+1_3368-1)del	No protein name	CFTRdele16-17b	CF-causing
c.2909G>A	p.Gly970Asp	G970D	CF-causing
c.2930C>T	p.Ser977Phe	S977F	Varying clinical consequence
c.2936A>T	p.Asp979Val	D979V	CF-causing
c.2998delA	p.Ile1000LeufsX2	3130delA	CF-causing
c.2988G>A	No protein name	3120G->A	CF-causing
c.(2988+1_2989-1)_(3367+1_3368-1)del	No protein name	CFTRdele17a,17b	CF-causing
c.(2988+1_2989-1)_(3468+1_3469-1)del	No protein name	CFTRdele17a-18	CF-causing
c.2988+1G>A	No protein name	3120+1G->A	CF-causing
c.2989-1G>A	No protein name	3121-1G->A	CF-causing

c.2989-2A>G	No protein name	3121-2A->G	CF-causing
c.2989-977_3367+248del	No protein name	3121-977_3499+248del2515	CF-causing
c.2991G>C	p.Leu997Phe	L997F	Non CF-causing
c.3002_3003delTG	p.Val1001AspfsX45	3132delTG	CF-causing
c.3017C>A	p.Ala1006Glu	A1006E	CF-causing
c.3011_3019delCTATAGCAG or c.3009_3017delAGCTATAGC	p.Ala1004_Ala1006del	3143del9	CF-causing
c.3039delC	p.Tyr1014ThrfsX9	3171delC	CF-causing
c.3039dupC	p.Tyr1014LeufsX33	3171insC	CF-causing
c.3041A>G	p.Tyr1014Cys	Y1014C	Unknown significance
c.3047T>C	p.Phe1016Ser	F1016S	Varying clinical consequence
c.3067_3072delATAGTG	p.Ile1023_Val1024del	3199del6	CF-causing
c.3080T>C	p.Ile1027Thr	I1027T	Non CF-causing
c.3095A>G	p.Tyr1032Cys	Y1032C	Varying clinical consequence
c.3103C>T	p.Gln1035X	Q1035X	CF-causing
c.3107C>A	p.Thr1036Asn	T1036N	CF-causing
c.3124C>T	p.Gln1042X	Q1042X	CF-causing
c.3139_3139+1delGG	p.Gly1047GlnfsX28	3271delGG	CF-causing
c.(3139+1_3140-1)_(3367+1_3368-1)del	No protein name	CFTRdele17b	CF-causing
c.3140-26A>G	No protein name	3272-26A->G	CF-causing
c.3154T>G	p.Phe1052Val	F1052V	Varying clinical consequence
c.3158C>T	p.Thr1053Ile	T1053I	Non CF-causing
c.3160C>G	p.His1054Asp	H1054D	CF-causing
c.3181G>C	p.Gly1061Arg	G1061R	CF-causing
c.3194T>C	p.Leu1065Pro	L1065P	CF-causing
c.3196C>T	p.Arg1066Cys	R1066C	CF-causing
c.3197G>A	p.Arg1066His	R1066H	CF-causing

c.3205G>A	p.Gly1069Arg	G1069R	Varying clinical consequence
c.3208C>T	p.Arg1070Trp	R1070W	Varying clinical consequence
c.3209G>A	p.Arg1070Gln	R1070Q	Varying clinical consequence
c.3217dupT	p.Tyr1073LeufsX3	3349insT	CF-causing
c.3222T>A or c.3220T>C or c.3222T>G	p.Phe1074Leu	F1074L	Varying clinical consequence
c.3230T>C	p.Leu1077Pro	L1077P	CF-causing
c.3266G>A	p.Trp1089X	W1089X	CF-causing
c.3276C>A or c.3276C>G	p.Tyr1092X	Y1092X	CF-causing
c.3292T>C	p.Trp1098Arg	W1098R	CF-causing
c.3293G>A or c.3294G>A	p.Trp1098X	W1098X	CF-causing
c.3294G>C or c.3294G>T	p.Trp1098Cys	W1098C	CF-causing
c.3297C>A	p.Phe1099Leu	F1099L	Varying clinical consequence
c.3302T>A	p.Met1101Lys	M1101K	CF-causing
c.3302T>G	p.Met1101Arg	M1101R	CF-causing
c.3304A>T	p.Arg1102X	R1102X	CF-causing
c.3310G>T	p.Glu1104X	E1104X	CF-causing
c.3353C>T	p.Ser1118Phe	S1118F	CF-causing
c.3365delC	p.Thr1122LysfsX12	3497delC	CF-causing
c.(3367+1+3368-1)_(3468+1_3469-1)del	No protein name	CFTRdele18	CF-causing
c.3368-2A>G	No protein name	3500-2A->G	CF-causing
c.3382A>T	p.Arg1128X	R1128X	CF-causing
c.3435G>A	p.Trp1145X	W1145X	CF-causing
c.3454G>C	p.Asp1152His	D1152H	Varying clinical consequence
c.3458T>A	p.Val1153Glu	V1153E	Varying clinical consequence

c.3468G>A	No protein name	3600G->A	CF-causing
c.(3468+1_3469-1)_(3717+1_3718-1)del	No protein name	CFTRdele19	CF-causing
c.(3468+1_3469-1)_(3963+1_3964-1)del	No protein name	CFTRdele19-21	CF-causing
c.3468+2dupT	No protein name	3600+2insT	CF-causing
c.3468+5G>A	No protein name	3600+5G->A	CF-causing
c.3472C>T	p.Arg1158X	R1158X	CF-causing
c.3475T>C	p.Ser1159Pro	S1159P	CF-causing
c.3476C>T	p.Ser1159Phe	S1159F	CF-causing
c.3484C>T	p.Arg1162X	R1162X	CF-causing
c.3485G>T	p.Arg1162Leu	R1162L	Non CF-causing
c.3528delC	p.Lys1177SerfsX15	3659delC	CF-causing
c.3532_3535dupTCAA	p.Thr1179IlefsX17	3667ins4	CF-causing
c.3587C>G	p.Ser1196X	S1196X	CF-causing
c.3600delA	p.Asp1201MetfsX10	3732delA	CF-causing
c.3605delA	p.Asp1202AlafsX9	3737delA	CF-causing
c.3611G>A or c.3612G>A	p.Trp1204X	W1204X	CF-causing
c.3659delC	p.Thr1220LysfsX8	3791delC	CF-causing
c.3691delT	p.Ser1231ProfsX4	3821delT	CF-causing
c.3700A>G	p.Ile1234Val	I1234V	CF-causing
c.3705T>G	p.Ser1235Arg	S1235R	Non CF-causing
c.3717G>A	No protein name	3849G->A	CF-causing
c.3717+4A>G	No protein name	3849+4A->G	CF-causing
c.3717+5G>A	No protein name	3849+5G->A	CF-causing
c.3717+40A>G	No protein name	3849+40A->G	CF-causing
c.3718-2477C>T	No protein name	3849+10kbC->T	CF-causing
c.3718-1G>A	No protein name	3850-1G->A	CF-causing
c.3718-3T>G	No protein name	3850-3T->G	CF-causing
c.3719T>G	p.Val1240Gly	V1240G	CF-causing
c.3731G>A	p.Gly1244Glu	G1244E	CF-causing
c.3737C>T	p.Thr1246Ile	T1246I	Varying clinical consequence

c.3744delA	p.Lys1250ArgfsX9	3876delA	CF-causing
c.3745G>A	p.Gly1249Arg	G1249R	CF-causing
c.3747delG	p.Lys1250ArgfsX9	3878delG	CF-causing
c.3752G>A	p.Ser1251Asn	S1251N	CF-causing
c.3761T>G	p.Leu1254X	L1254X	CF-causing
c.3763T>C	p.Ser1255Pro	S1255P	CF-causing
c.3764C>A	p.Ser1255X	S1255X	CF-causing
c.3773dupT	p.Leu1258PhefsX7	3905insT	CF-causing
c.3806T>A	p.Ile1269Asn	I1269N	CF-causing
c.3808delG	p.Asp1270MetfsX8	3940delG	CF-causing
c.3808G>A	p.Asp1270Asn	D1270N	Varying clinical consequence
c.3822G>A	p.Trp1274X	W1274X	CF-causing
c.3846G>A	p.Trp1282X	W1282X	CF-causing
c.[3846G>A;3848G>T]	p.[Trp1282X;Arg1283Met]	W1282X;R1283M	CF-causing
c.3848G>T	p.Arg1283Met	R1283M	CF-causing
c.3872A>G	p.Gln1291Arg	Q1291R	Varying clinical consequence
c.3873G>C	p.Gln1291His	Q1291H	Varying clinical consequence
c.3873+1G>A	No protein name	4005+1G->A	CF-causing
c.(3873+1_3874-1)_(3963+1_3964-1)del	No protein name	CFTRdele21	CF-causing
c.3873+2T>C	No protein name	4005+2T->C	CF-causing
c.3883_3886delATTT	p.Ile1295PhefsX32	4010del4	CF-causing
c.3883delA	p.Ile1295PhefsX33	4015delA	CF-causing
c.3889dupT	p.Ser1297PhefsX5	4016insT	CF-causing
c.3891dupT	p.Gly1298TrpfsX4	4022insT	CF-causing
c.3908delA	p.Asn1303ThrfsX25	4040delA	CF-causing
c.3909C>G	p.Asn1303Lys	N1303K	CF-causing
c.3929G>A	p.Trp1310X	W1310X	CF-causing
c.3937C>T	p.Gln1313X	Q1313X	CF-causing

c.(3963+1_3964-1)_(*1_?)del	No protein name	CFTRdele22-24	CF-causing
c.3964-78_4242+577del	No protein name	CFTRdele22,23	CF-causing
c.3971T>C	p.Leu1324Pro	L1324P	CF-causing
c.3988C>T	p.Gln1330X	Q1330X	CF-causing
c.4004T>C	p.Leu1335Pro	L1335P	CF-causing
c.4036_4042del	p.Leu1346MetfsX6	4168delCTAAGCC	CF-causing
c.4046G>A	p.Gly1349Asp	G1349D	CF-causing
c.4077_4080delTGTTinsAA	No protein name	4209TGTT->AA	CF-causing
c.4086dupT	p.Lys1363X	4218insT	CF-causing
c.4097T>A	p.Ile1366Asn	I1366N	CF-causing
c.4111G>T	p.Glu1371X	E1371X	CF-causing
c.4124A>C	p.His1375Pro	H1375P	CF-causing
c.4127_4131delTGGAT	p.Leu1376SerfsX8	4259del5	CF-causing
c.4144C>T	p.Gln1382X	Q1382X	CF-causing
c.4147dupA	p.Ile1383AsnfsX3	4279insA	CF-causing
c.4197_4198delCT	p.Cys1400X	4326delTC	CF-causing
c.4231C>T	p.Gln1411X	Q1411X	CF-causing
c.4234C>T	p.Gln1412X	Q1412X	CF-causing
c.4242+1G>T	No protein name	4374+1G->T	CF-causing
c.4242+1G>A	No protein name	4374+1G->A	CF-causing
c.4251delA	p.Glu1418ArgfsX14	4382delA	CF-causing
c.4300_4301dup	p.Ser1435GlyfsX14	4428insGA	CF-causing
c.4364C>G	p.Ser1455X	S1455X	Varying clinical consequence
c.4426C>T	p.Gln1476X	Q1476X	Varying clinical consequence
c.4439T>C	p.Leu1480Pro	L1480P	Varying clinical consequence

Appendix 14 – Hot weather advice

The movement of salt and fluid through the cells in the body is altered in cystic fibrosis. This means high levels of salt can be lost through sweating. This is especially important to consider in hot weather and even more so if a child is running around a lot or exercising. Your child will sweat more, meaning the sodium level in the body can drop quite quickly, and this also increases the risk of dehydration. The amount of salt loss would seem to be reduced by Kaftrio.

Symptoms of salt depletion

- Feeling tired
- Lethargic (floppy in infancy)
- Thirsty
- Finding it difficult to concentrate
- Headaches
- Irritable
- Loss of appetite
- Feeling sick or vomiting
- Cramps in limbs
- Sunken eyes

If your child vomits, has sunken eyes (dark circles) or is lethargic or floppy it is very important that you seek medical advice straight away as these are signs of DEHYDRATION or even HEATSTROKE.

Prevention of salt depletion

When travelling to very hot dry countries, or when the weather in the UK is particularly hot and dry it is vital to give additional salt and fluids to ensure the sodium levels remain normal.

These are some of the ways you can help:

- Keep out of the sun between the hours of 11am and 3pm.
- Provide opportunities for rest during the hottest time of the day.
- Infants: Dioralyte (or equivalent) sachets are ideal. Dioralyte is for oral rehydration and can be bought over the counter in chemists and supermarkets.
- Children: Ensure your child drinks plenty of fluid. Water, dioralyte and isotonic sports drinks are all good options. If choosing sports drinks, opt for the 'light' versions for smaller children as these have lower sugar content.
- Encourage your child to wear a hat and use usual precautions to avoid sunburn, including high factor sun cream.
- Add extra salt to your child's food and give them salty snacks like crisps, marmite and cheese.

Salt supplements

Salt supplements are available as a way of giving extra salt to children with CF. These are very effective when children are feeling tired or getting cramps due to hot weather.

- **Infants 0 – 12 months**: Up to 2 sachets of Dioralyte or an equivalent oral rehydration solution per day. Each Dioralyte sachet is mixed with 200mls of water (use cooled boiled water if under 6 months). Once made up, Dioralyte can be kept in the fridge for 24 hours.

This can be easier to achieve by giving 100ml twice a day to younger babies. For other oral rehydration solutions follow the manufacturers recommendations for the preparation and storage of solutions.

- **Children 1 - 7 years old**: 2 sodium chloride 600mg MR tablets (Slow Sodium, containing 10mmol sodium per tablet) per day during hot weather. For those who will not take tablets, Dioralyte or an equivalent oral rehydration solution can be used - usually 2–4 sachets per day.

- **Children over 7 years old**: 2 – 4 sodium chloride 600mg MR tablets (Slow Sodium, containing 10mmol sodium per tablet) per day during hot weather. Can also have Dioralyte or an equivalent oral rehydration solution.

Drugs & the sun
By the way, don't forget some drugs sensitise the skin to sun burn *e.g.,* ciprofloxacin, doxycycline and voriconazole, so very high factor sun cream MUST be used.

If you have any concerns or questions about salt loss or managing in hot weather, please contact the CF Team. If you are travelling to a hot country it is important to let the team know as soon as possible to plan supplements if needed.

Appendix 15 – Travel letters

Royal Brompton Hospital
Sydney Street
London SW3 6NP

Main switchboard: +44 (0)20 7352 8121

Date:

TO WHOM IT MAY CONCERN

Dear Sir/Madam,

Re:

This 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 liquids, 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; or after 5pm phone 0207-352 8121 and ask for bleep 1237 (on call paediatric respiratory SpR).

Yours faithfully,

PRINT NAME:

Signed:

Date:

Royal Brompton Hospital
Sydney Street
London SW3 6NP

Main switchboard: *+44 (0)20 7352 8121*

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; or after 5pm phone 0207-352 8121 and ask for bleep 1237 (on call paediatric respiratory SpR).

Yours faithfully,

PRINT NAME:

Signed:

Date:

Royal Brompton Hospital
Sydney Street
London SW3 6NP

Main switchboard: *+44 (0)20 7352 8121*

Date:

TO WHOM IT MAY CONCERN

Dear Sir/Madam,

Re:

This 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.

The child also has diabetes. It is essential that the family carry diabetic equipment for blood glucose monitoring (including a lancet drum) and medication (insulin pens with needles) in their hand luggage.

If any further information is required, please do not hesitate to contact the department at the Royal Brompton Hospital on 0207-351 8755; or after 5pm phone 0207-352 8121 and ask for bleep 1237 (on call paediatric respiratory SpR).

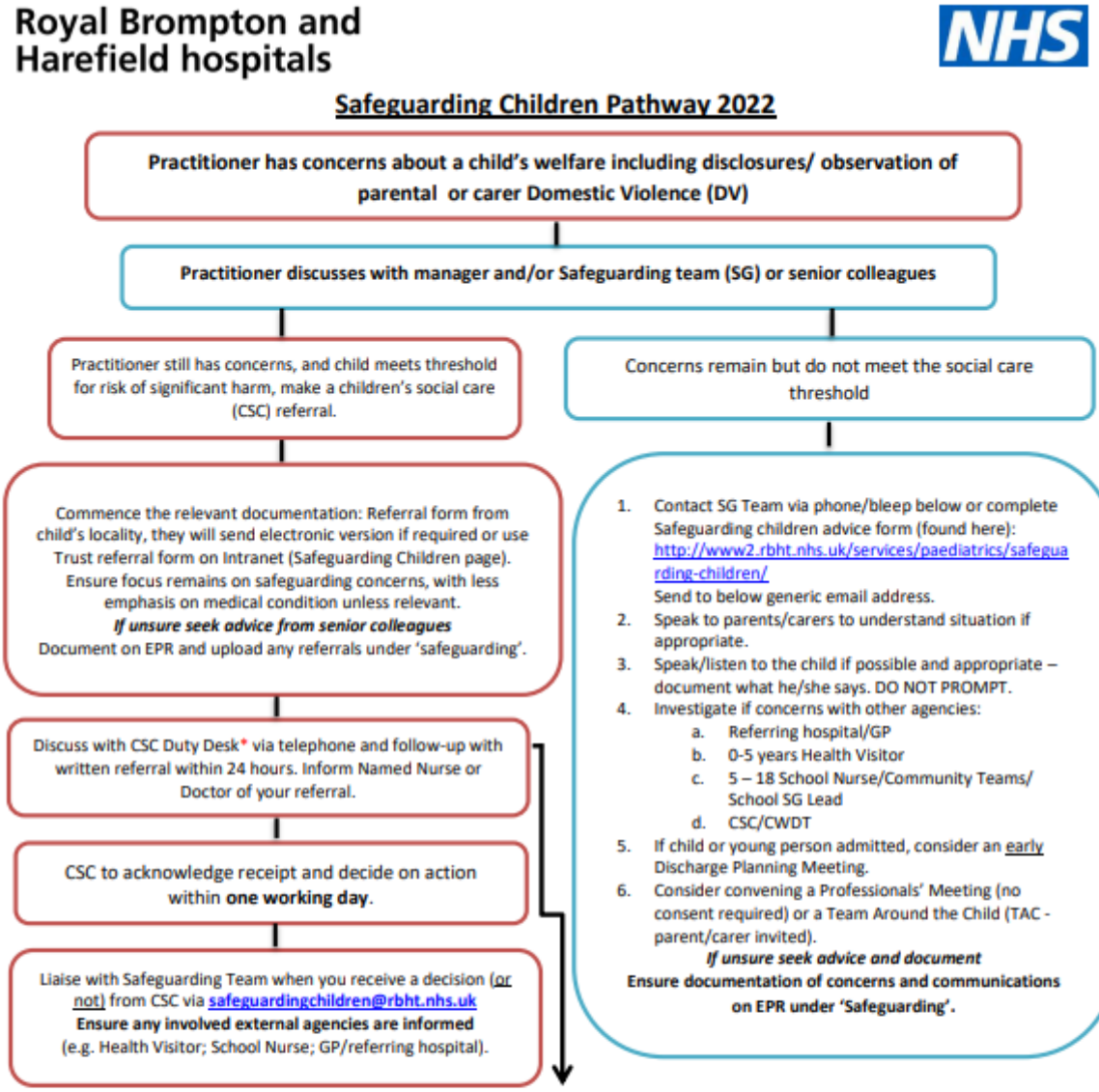
Yours faithfully,

PRINT NAME:

Signed:

Date:

Appendix 16 – Safeguarding children pathway



SAFEGUARDING ADVICE CONTACTS – Email: Safeguardingchildren@rbht.nhs.uk		
Name	**Role**	**Contact ☎ Internal: 0330 128 8121**
	Safeguarding Children Team	ext. 82903/ 82904/ 84289
	Safeguarding Children Team Mobiles	07896 220 697 / 07484 926 928 / 07929 792 359
Rachel Ward	Safeguarding Children Administrator	ext. 84304
Michele Puckey	Deputy Lead Clinician for Safeguarding Children	ext. 84130 07791 547 750 Bleep: 1228
Jonathan Penny	Named Doctor Safeguarding Children	0796 075 4872
Frank Butau	Safeguarding Adults & Learning Disabilities Lead	ext. 84195 07484 037301 Bleep: 6287 Email: Safeguardingadults@rbht.nhs.uk
Social Worker (SW) Teams:		
Chelsea & Westminster Hospital SW Team:	**☎020 3315 1316**	**Out of hours ☎ 020 7373 2227**
Hillingdon Social Work Team	**☎01895 556 633**	**Out of hours ☎ 01895 250 111**
Westminster SW Team Email:	**accesstochildrensservices@westminster.gov.uk**	**Out of hours ☎ 0207 641 6001**

Updated: Jan 2022

Appendix 17 - Form for CF Focus meeting

Paediatric Cystic Fibrosis Team

Complex CF MDT Meeting

Date: Time:

Present:

Apologies:

Patient		**Hospital No**		**DOB:**	
Consultant		**Next Clinic**			
Diagnosis					
CONSULTANT					
CNS					
PHYSIO					
PHARMACY					
PSYCHOLOGY					
DIETICIAN					
SAFEGUARDING					
WARD SISTER					
PLAY THERAPIST					
Points of discussion from the MDT					
Plan (action points) and ownership of task					
•					

Appendix 18 - Social security benefits

IMPORTANT: Please check whether you are eligible for benefits before submitting a claim. Your residency and eligibility status can affect whether you are entitled to support. Contact a benefits advisor if you are uncertain.

We would recommend contacting a benefits advisor to find out what else you and your family might be entitled to.

1. Disability Living Allowance (DLA) - for children up to the age of 16

Disability Living Allowance (DLA) provides help with the extra costs of bringing up a child with disability, if they have difficulties walking, or need much more looking after than other children of the same age, due to their disability or condition. DLA is not means-tested, so your income or savings will not be considered, and you don't have to pay any tax on it. DLA can entitle you to other types of support too.

The best way to make a new claim for DLA is to call 0800 121 4600 (Monday to Friday, 9am to 5pm) to order an application form [call charges]. If you return the completed application form within 6 weeks, and are awarded DLA, those DLA payments can be paid back to when you ordered the application form on the phone.

You can also download an application form to fill out, but the start date of the claim will be the date the form is received.

You can read the most up to date information about DLA on the government website, and read more hints and tips on the Cystic Fibrosis Trust website.

Terminal Illness - There are special rules for claiming DLA if a child might have less than 6 months to live, so that they can get DLA more quickly, and don't have to fill out every page of the application form. You will need to ask your doctor, or another healthcare professional to fill out a medical report form called a DS1500. Don't wait for the DS1500 form to be completed before ordering your DLA claim form, we recommend ordered the DLA claim form over the telephone so that you can receive a back-payment to when the form was ordered.

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 three different rates: a lower rate, a middle rate, or a highest rate, depending upon how much help and supervision is required because of the child's disability. 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, for children aged 5 or over who need extra guidance or supervision walking outdoors. This is paid at two different rates: the lower weekly rate, and the higher weekly rate. The higher rate can be paid from the age of 3 years, the lower rate can be paid from the age of 5 years. The higher weekly rate of the Mobility part of DLA can be exchanged for lease of a vehicle through the Motability scheme. If your child has mobility difficulties, they may also qualify

for a Blue Badge. If your child gets the higher weekly rate of the Mobility part of DLA, they will automatically qualify for a Blue Badge.

TOP TIPS

1. You can claim and receive payment from DLA while your child is in hospital.

2. It might be useful to keep a diary for a few days to note what type of care your child requires (both day and night) and how much time this takes. This is because the DLA application needs to show what extra care and help your child needs because of their disability or sickness.

3. The application form is long. It is a good idea to get help to fill out the application. The Cystic Fibrosis Trust have a helpline (0300 373 1000 or 020 3795 2184) that you can contact them for assistance on (Monday to Friday 10am to 4pm) and they also have a dedicated email help service too (helpline@cysticfibrosis.org.uk).

4. A local advisor might be able to help you to fill out the application form too. You can search for local Benefits advisors here.

Keep a photocopy of the application form before you send it. Send supporting evidence, but don't send your original documents, as DLA won't be able to send these back to you.

When a child who receives DLA turns 16, they will be sent a letter inviting them to claim Personal Independence Payment (PIP). If the child was in hospital when they turned 16, they won't be invited to claim PIP until after they leave hospital. If the child was awarded DLA under the special rules for terminal illness, they will be invited to claim PIP about 20 weeks before their DLA claim ends. Your child's DLA payments will stop unless they apply for PIP by the date in their invitation letter, they will continue to receive DLA until their PIP claim is assessed.

2. Personal Independence Payment (PIP) - for children aged 16 and above

Personal Independence Payment (PIP) can provide help with the extra costs of living with a long-term health condition or disability, for people who have difficulties getting around, or with daily living. PIP is not means-tested, so your income or savings will not be considered, and you don't have to pay any tax on it. PIP can entitle you to other types of support too.

You can claim PIP by calling the new claims line (0800 917 2222, Monday to Friday, 8am to 5pm) [call charges]. At this stage you will just need to provide basic information like your contact details, National Insurance number, time spent in hospitals or residential care, and bank account details for PIP to be paid into if awarded. After you contact PIP you will be sent a personalised form to fill out. You might be invited to an assessment with an independent health professional, this could be at an assessment centre, or in your own home.

You can also claim by writing to PIP at 'Personal Independence Payment New Claims, Post Handling Site B, Wolverhampton, WV99 1AH' but it will delay your claim.

You can read the most up to day information about PIP on the government website, and read more hints and tips on the Cystic Fibrosis Trust website.

Terminal Illness - There are special rules for claiming PIP if you are not expected to live more than 6 months, so that you can get PIP more quickly. You will need to ask your doctor, or another healthcare professional to fill out form DS1500.

There are two parts to PIP

- **Daily living part** – if you need help more than half of the time with daily tasks. These include things like preparing food, taking nutrition, using the toilet, washing and bathing, dressing and undressing, reading, communicating and managing medicines or treatments. This is paid at two different rates: the lower weekly rate and the higher weekly rate.
- **Mobility part** – if you need help to move around, and/or plan and follow journeys. This is paid at two different rates: the lower weekly rate and the higher weekly rate. The higher weekly rate of the Mobility part of PIP can be exchanged for lease of a vehicle through the Motability scheme. If your child has mobility difficulties, they may also qualify for a Blue Badge. If your child gets the higher weekly rate of the Mobility part of PIP, they will automatically qualify for a Blue Badge.

TOP TIPS

1. You can claim and receive payment from PIP while your child is in hospital, if their admission began before they turned 18. If your child is above the age of 18, their PIP will end after they've been in hospital for 28 days.
2. PIP has a point scoring system on each question and looks at your ability to carry out different activities. You can contact The Cystic Fibrosis Trust for a copy of the 'descriptors' of abilities to carry out activities. You might find this a helpful indicator of how many points you might get. The Cystic Fibrosis Trust can help you to identify which descriptors might apply to you and might be able to write you a supporting letter based on these.

3. The application form is long. It is a good idea to get help to fill out the application. The Cystic Fibrosis Trust have a helpline (0300 373 1000 or 020 3795 2184) that you can contact them for assistance on (Monday to Friday 10am to 4pm) and they also have a dedicated email help service too (helpline@cysticfibrosis.org.uk).

4. A local advisor might be able to help you to fill out the application form. You can search for local Benefits advisors here.

5. Keep a photocopy of the application form before you send it.

6. Send supporting evidence. It's a good idea to get a supporting letter. You might be able to get a supporting letter from a health care professional, or from the Cystic Fibrosis Trust. Don't delay sending in your application form if you haven't got a supporting letter yet, you can send in medical evidence later.

3. Carer's Allowance

If a child receives either middle or higher rate of DLA care component, or either rate of the daily living component of PIP, someone who cares for them for at least 35 hours a week may be able to claim Carers Allowance. Carers Allowance is taxable, but this will notgenerally won't affect you unless you have other sources of taxable income, such as occupational or personal pensions or part time earnings which bring your combined income above the personal allowance.

You can read more about the eligibility criteria for claiming Carers Allowance on the government website.

N.B Applying for benefits and appeals against decisions can be complex and we recommend that families access appropriate specialist advice, from a local benefits advisor or the Cystic Fibrosis Trust.

4. Charities

The Family Fund is the UK's largest charity providing grants for families raising disabled or seriously ill children and young people. Families can apply for clothing, breaks and days out, computers and tablets, furniture and white goods, sensory toys and equipment, games, books, specialist trikes or bikes and garden improvements, amongst other items and services.
The Family Fund may be able to offer a grant once every 18 months. You can find out more about eligibility criteria for a Family Fund grant, and how to apply, on their website.

The Cystic Fibrosis Trust offer a range of grants to people with Cystic Fibrosis, including towards emergencies, holidays, health and wellbeing and other needs. You can read more about these on the grants page of their website.

The charity Turn2us have a grants search tool on their website, which you can use to find grants that you and your family may be eligible to apply for.

The Disability Grants website also has a range of information about different charities that you may be eligible to apply for.

Appendix 19 – CF Trust consensus documents, factsheets & leaflets

These are available on the CF Trust website – Publications (cysticfibrosis.org.uk). Press ctrl+click on titles.

Consensus Documents

Some of these are quite old and mya not reflect latest consensus.

European Cystic Fibrosis Society Standards of Care Available in Open Access

HS National Programmes of Care and Clinical Reference Groups, Internal Medicine – Group A, A01 Cystic Fibrosis

Guidelines on NTM infection issued by Thorax.

M Abscessus guidelines. November 2017 (amended March 2018).

Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis. Fourth edition. November 2020.

Nutritional Management of Cystic Fibrosis. September 2016.

Standards for the Clinical Care of Children and Adults with Cystic Fibrosis in the UK. Second edition. December 2011.

Pharmacy Standards of Care. November 2011

Laboratory Standards for Processing Microbiological Samples from People with Cystic Fibrosis. First edition. September 2010.

Antibiotic Treatment for Cystic Fibrosis. Third edition. May 2009.

Methicillin-resistant Staphylococcus aureus (MRSA). April 2008.

European cystic fibrosis bone mineralisation guidelines. February 2011.

Pseudomonas aeruginosa infection in people with Cystic Fibrosis. Suggestions for Prevention and Infection Control. Second Edition. November 2004.

The Burkholderia cepacia Complex - Suggestions for Prevention and Infection Control. Second edition. September 2004.

Management of Cystic Fibrosis-related Diabetes Mellitus. June 2004.

National Consensus Standards for the Nursing Management of Cystic Fibrosis. May 2001.

Factsheets, information packs and publications –

https://www.cysticfibrosis.org.uk/the-work-we-do/publications/factsheets-and-information-packs. This takes you to the contents page where direct links are available.

Additionally, if you click on the topics below, it takes you to the direct links, often to several issues, relevant to that topic.

- Bereavement
- Body image
- CF-related conditions
- Diagnosis
- Education and work
- End of life planning
- Family planning
- Festival planning
- Money and benefits
- Moving from paediatric to adult care (transition)
- Nutrition
- Physiotherapy
- Resources for children
- Taking part in clinical trials
- Transplants
- Treatments, therapies and care (including physiotherapy)

Appendix 20 – Useful telephone numbers ☎

Royal Brompton Hospital - 0207 352 8121

	Extensions
Admissions paediatric coordinator	82118, 88556, 82371, bleep 1256
Bed Manager (Rose ward)	88588, bleep 7078
Biochemistry	88411
Bone densitometry	88666
CF Secretary	88674
Dietitian	88465, bleep 7101
Foulis ward (adults)	88069, 84070
Haematology	88406
LCI	88233
Lung function	88910
Microbiology	88451
Nuclear medicine	
-- Bone densitometry	88666
-- Ventilation Scans	88666
Pharmacist (paediatric)	84375, bleep 7403, 7410 or 7425
Pharmacy (dispensary)	88038, 87777
Physiotherapy	88088, 88436 bleep 7300, 7304, 7311
Rose Ward	82411, 82412, 82413, 88543
Ventilation Scans	88666
X-ray (Sydney St – in patients)	82326
X-ray (Fulham Wing – clinic)	84668
X-ray PACS	88275

External numbers

CF Trust	020 3795 1555 1, Aldgate, London EC3N 1RE www.cysticfibrosis.org.uk
CF Foundation (USA)	www.cff.org
UK Health Security Agency (formerly PHE) Colindale	0208 200 4400 61 Colindale Avenue, London NW9 5EQ