8. Other non-pulmonary complications of CF

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8.1 Cystic Fibrosis-Related Diabetes

Contacts

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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 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 also 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)
- Oral glucose tolerance test
- Random glucose tests
- HbA1c

When to test for glucose status in CF:

Current CF Trust recommendation is for OGTT 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.
- Before high dose steroids, starting overnight feeds, or before major surgery.
- If there are documented hypoglycaemic episodes or symptoms suggesting this.

CGMS

How it works - A subcutaneous sensor measures the glucose in the interstitial fluid and gives a continuous profile of glucose levels for up to 6 days. The sensor needs to be calibrated with blood glucose measurements at least three to four times a day for as long as the sensor is in place, and the profile can be downloaded at the end of the study. The equipment gives a profile and statistical breakdown of the glucose levels.

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.
- Blood glucose still needs to be measured 3-4 times in a 24-hour period which can be a problem with needle anxiety.
- Sensor insertion can be uncomfortable
- Clear guidelines as to when to treat on the basis of CGMS are not available.
- 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.

Profile of capillary glucose tests

Checking random glucose levels over a few weeks can give a good picture of glucose status. Draw up a clear plan of how many tests are needed (ideally 3- 4/day) and when to do them. Testing should be before, and also 1-2 hours after meals. The most likely time for glucose to be high is about 2 hours after the evening meal. In CF fasting (pre breakfast) glucose levels can be normal even if the glucose levels later in the day are very high.

When to use random glucose profile
- If CGMS is not possible, or as an outpatient screen for glucose status.
- Ward admissions

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

Disadvantages

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

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

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 (or a profile of capillary glucose levels) 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 levels

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.

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 high calorie and high fat diet must continue. Older children should avoid high sugar snacks and drinks between meals (*i.e.* regular fizzy drinks, juices and squashes, jellied sweets etc.) and substitute no-sugar-added drinks (*i.e.* diet fizzy drinks and squashes).

Regular eating: Encourage regular meals and snacks (including breakfast if possible) because this makes the diabetes easier to control and improves weight gain. Food intake should not be reduced to try to control glucose levels; meals and snacks must be given whatever the blood glucose.

Psychology referral is suggested as this is a stressful time for the child and family with added treatment burden and possibly 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 on. Chocolate and sweets are not a good alternative for the initial treatment of hypoglycaemia- they are not as rapidly absorbed as glucose, and it gives the wrong psychological message to reward hypoglycaemic episodes. If the test before a dose of insulin shows hypoglycaemia, treat the hypoglycaemia and then go ahead with the meal and give the normal insulin. Do not treat as hypoglycaemia unless glucose levels <4 mmol/l.

- If hypoglycaemia is suspected test the blood glucose if possible.
- Treat hypoglycaemia with 10g of rapidly absorbed carbohydrate (100ml of Lucozade, 100 ml of Coca-Cola, 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 (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 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 of the local team are aware of the management of CFRD. Nicola Bridges or Saji Alexander are always happy to discuss these patients and ideally, we should review them at the Brompton as well. We give families our contact details and they can phone or e mail with problems.

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

Monitoring
A realistic plan for monitoring blood glucose levels at home should be discussed. 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 recently 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. 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 review the patient, even if things appear to be going well. 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 the word "units" must be written in full and never "u" or "iu". This is a cause of drug errors because a badly written "u" can be taken to be a zero.

Safe insulin administration

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

Surgery

Many individuals with CF related diabetes are able to 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: 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 13). 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 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, as a result of sex steroid action. CF patients are at increased risk of low bone density and it makes sense to optimise it at this point.

Treatments available

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

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 www.bsped.org.uk).

8.4 Bone Metabolism

Bone density in CF

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

- **Steroids** Frequent courses of oral or intravenous steroids and those on high dose inhaled corticosteroids.

- **Vitamin D and Calcium** are vital in bone growth**. Everyone** with CF (including pancreatic sufficient) should take vitamin D supplements, (see below for management of deficiency). Encourage intake of 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 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 multivitamin which is prescribed to all CF children, regardless of pancreatic status.

- **Infection**- chronic inflammation can inhibit bone formation.

- **Endocrine issues** - sex steroids are vital in the attainment of adult bone density during puberty and adult levels of sex steroids are required to prevent osteoporosis in adults.
- **Physical activity -**exercise, particularly weight bearing is needed for normal bone growth and children who do not move much will have reduced bone density.

- **CFTR** is expressed in bones and mutations in CF may contribute to reduced bone density.

- **CFRD** may be a potential risk factor for reduced bone density.

Screening of bone density

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.

Repeat the scan earlier if:
- **BMD z score is -1 to -2, repeat in 2 years**
- **BMD z score is less than -2.0, 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
- Assessment of sex steroid levels in adults
- Encouragement of weight bearing exercise

Management of reduced bone density and osteoporosis

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

- *Pubertal delay and hypogonadism* Consider treatment with sex steroids if bone density is reduced in an adolescent with pubertal delay and assess whether adult levels of sex steroids have been achieved in post pubertal individuals.
- *Clinical factors* - CFRD, reduced lung function (FEV_1<50% predicted), nutrition, immobility.
- *Vitamin D and calcium* status.

Bisphosphonate treatment
Bisphosphonates reduce turnover and result in increased bone density. There have been several studies of bisphosphonates in adults and young people with CF demonstrating increased bone density with treatment. Bisphosphonates have been demonstrated to decrease fracture risk in a range of other clinical situations but data in CF is lacking. Zoledronic acid, given once or twice a year as an intravenous infusion would be our choice of bisphosphonate in all ages. There are several oral formulations, but there are significant cautions about how the tablets should be taken which may limit use in children, and there are no liquid preparations.

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

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

Potential side effects of bisphosphonates:

- Osteonecrosis of the jaw can occur and those with poor dental hygiene are at most risk. A dental check is mandatory prior to start of bisphosphonates.
- There is an increased risk of atypical fractures of the femur.
- Bone pain and flu like symptoms - studies using IV bisphosphonates suggest these may be more common in CF.
- 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.

Vitamin D status

We measure total 25 hydroxy-vitamin D levels annually. Because a large proportion of vitamin D comes from sunlight, levels are lower in winter and spring. Low vitamin D levels are very common in the general population (poor diet, pigmented skin and covering clothing

are risk factors). Aim to maintain a serum 25 hydroxy-vitamin D level over 75nmol/l to optimise bone health.

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

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

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

Prophylaxis to prevent deficiency

400 IU of vitamin D daily should prevent deficiency in most infants and 800 IU in older children.

10 mcg of colecalciferol is equivalent to 400 units.

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

Treatment of vitamin D deficiency see formulary (section 11.2b)

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

Stoss therapy is our principle way of treating vitamin D deficiency. It involves oral administration of the total treatment dose of vitamin D given in a single dose. Ideally this is given in clinic. An alternative is the whole dose as a single intramuscular injection. This may need to be repeated (usually every 3 months) 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. See section 11.2b for doses.

Oral colecalciferol can still be given daily for 3 months but stoss therapy is likely to be more effective.

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

Do not increase the dose of DEKAs too much because there is a risk of Vitamin A toxicity. Vitamin D toxicity is rare and usually only occurs following massive miscalculations of the dose- individuals who are getting vitamin D from a number of sources such as supplements and fortified feeds are not going to develop toxicity. Combined calcium and vitamin D

preparations are very difficult to take, and the dose required to treat Vitamin D deficiency would be unlikely to be tolerated. Do not treat vitamin D deficiency with alfacalcidol.

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 William Grant (who has a particular specialisation in paediatric nasal problems), Consultant ENT Surgeon at Chelsea & Westminster Hospital (020 3315 7972). Mr Chadwan Al Yaghchi is present in the Brompton on the 2nd and 3rd Friday of every month from 9am-1pm and can see the children by agreement with him or the Airway Fellow, if there is an acute complication in an In-patient.

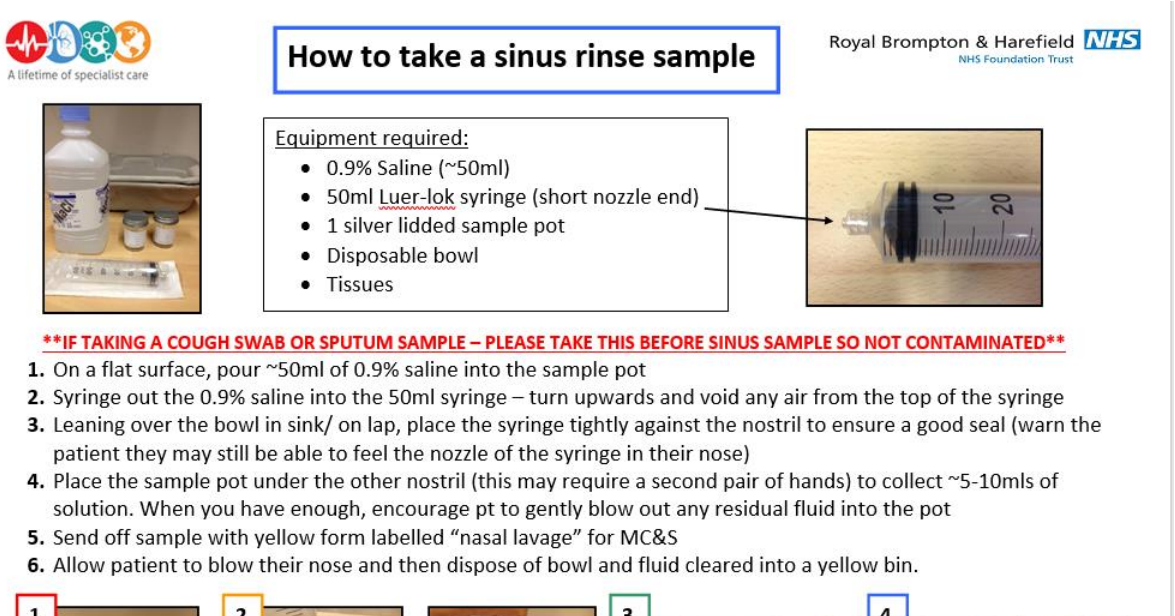
8.5b Sinusitis

- 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 (rhDNase, 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.
- RhDNase 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.

Nasal Rinse Sample for Bacterial Analysis:



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 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

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. Rh-DNase, 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 (Rh-DNase 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.

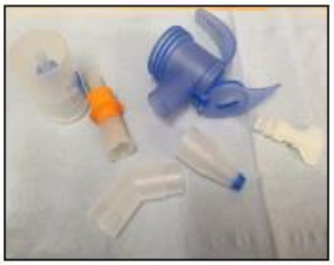
DNase (Pulmozyme) sinus neb

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.

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.

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. We will test this from April 2020, in all newly diagnosed infants at their 1st year annual review and catch up the whole clinic over the next 1-2 years. It will be added to the CF genetics panel so will be tested automatically in anyone having CF genetics tested at RBH. If positive, we will check the child's hearing, and we will try and avoid use of 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 now use oral N-acetylcysteine for all IV aminoglycoside course 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. There are still no published randomised controlled trials according to 2016 Cochrane review.

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

Occasionally, sero-positive **rheumatoid arthritis** occurs in CF. It may require treatment with anti-inflammatory agents, steroids and regular infusions of immunoglobulin (see section 6.12) re approval and funding).

Finally, it must be remembered that **ciprofloxacin** & **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 (tel 0207 829 7887) at Great Ormond Street Hospital for Children.

8.7 Pseudo-Bartter's syndrome

An uncommon cause of metabolic alkalosis that has been seen as a presenting feature of CF as well as a complication in those with known disease. It is accompanied by chronic salt depletion and sometimes 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! 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. 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.

Female fertility may be reduced due to thickened cervical mucus (note that women who are on ivacaftor have had their fertility improved), and the issue of pregnancy and CF can be discussed with Mr Guy Thorpe-Beeston, Consultant Gynaecologist at Chelsea & Westminster Hospital (0203 315 8000). Generally women with CF need to be relatively healthy when planning a pregnancy.

8.9 Stress incontinence

Urinary incontinence is a condition where certain activities *e.g.* coughing, laughing, jumping etc. lead to a leak of urine. This can be anything from a slight dribble to a complete emptying of the bladder. It is known that many women with CF are affected by urinary incontinence and it has become increasingly recognised that young girls may also be affected. This has been highlighted by the survey carried out at the Brompton, Great Ormond Street and Royal London hospitals, where we found 1 in 3 girls aged 11-17 years answering the survey had a problem at times. For many (if not all) girls this is rather embarrassing, and many do not want

to talk to their parents about it, and especially not to male doctors! It is more likely they will discuss this with female members of the team. Ensure there is no vaginal candidiasis as there is increased risk in presence of incontinence.

We can arrange for the girls to be seen by a gynaecologist and/or women's health physiotherapist, but initially they are seen by one of our physiotherapists, as sometimes simple 'pelvic floor exercises' and a technique known as 'the knack' (a pelvic floor contraction) can be quite helpful. In addition, bladder and posture management may also be recommended. Older children may find the NHS Squeezy App useful www.squeezyapp.co.uk. Useful patient information leaflets are available at https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/supporting-clinicians/resources-for-clinicians/physiotherapy-leaflets.

Please note that, although it is less common, stress urinary incontinence may also occur in males and for some patients (boys and girls) faecal incontinence may be an issue.