6. Respiratory care

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 out patients for a time slot but tell them to ring back if Appointments will not give them an appointment. If the family comes from a long way away, then consider using the local hospital, but brief whoever will see them there and ask for a report back. Some indications of chest exacerbation are:

- Increased cough, and in particular a new or increased 'wet' cough should always be taken seriously, 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, 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 or chloramphenicol) 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.

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 and also to ensure high levels of tissue and sputum penetration (see drug formulary section 11). Use the serious infection doses and round up not down. Do not prescribe silly volumes *e.g.* 3.44 ml - the nurses cannot measure them accurately, and neither can you. CF is a serious condition and the aim of therapy is to push antibiotic doses to the upper therapeutic range. When results of sputum culture are available, confirm that all organisms are covered by the chosen regimen. However, if the child is improving clinically on antibiotics to which the organisms exhibit *in vitro* resistance, do not automatically change them (but discuss with consultant). 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 (see para iv).

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

iii. If on no prophylaxis, you must prescribe an antibiotic, which will cover *S aureus* and *H influenzae*. 1st choice is treatment dose co-amoxiclav; acceptable alternatives would be a macrolide (clarithromycin or azithromycin), although microbial resistance (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. They must be given for **a minimum of 2 weeks, but carried on for at least 1 week once the child is symptom-free.** So, if for example, the child is completely well after the 1st week, then they can stop the antibiotics at 2 weeks. If it takes 2 weeks to become symptom free, the antibiotics can be stopped at 3 weeks. If, however the child is not symptom free at 2 weeks, the parents must contact the CF nurse specialist for assessment.

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

vi. 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.

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

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 (see above, 2.iv for details)
- 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 unknown 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.

Never had *P aeruginosa*	IV meropenem single agent.
No *P aeruginosa* for 3 years (must include last year off nebulised antibiotics)	IV meropenem 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. If *S aureus* is isolated within the last year, add in IV teicoplanin rather than

high dose oral flucloxacillin. Flucloxacillin is not used IV as it causes problems with IV lines and may cause backache.

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 & CF START study

- The question of staphylococcal prophylaxis is based on a few studies only and evidence for benefit is weak. Our previous policy was to start it in all newborn screened children, unless there was a compelling reason not to, *i.e.* not tolerated, or allergy. However we are now part of the CF START national study (www.cfstart.org.uk/) on the role of flucloxacillin prophylaxis, All parents of new-born screened babies are given a chance to be recruited within 1st 70 days of life (information given during education visit). If they are in the study, they are randomised to either 'PREVENT & TREAT' when they start prophylactic flucloxacillin at 125 mg BD (with the dose remaining unchanged until they finish the study at 4 years of age); or DETECT & TREAT in which case they are on no prophylaxis and have organisms treated when cultured. If the family do not want to be recruited, we expect them to have standard therapy which for us is flucloxacillin prophylaxis using the same dose – 125 mg BD.

- 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* in particular 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 at all possible for treatment) because of evidence implicating this class of antibiotics as causing a greater prevalence of infection with mucoid *P aeruginosa.*

Ib. Exacerbations

- Whether on flucloxacillin prophylaxis or not, give treatment dose for **4 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.

Ic. First isolation

- *In a well child* (clinical judgment) receiving flucloxacillin prophylaxis, we use oral co-amoxiclav for **4 weeks**.
- *In a well child* (clinical judgment) **not** receiving flucloxacillin prophylaxis, we use oral flucloxacillin for **4 weeks**.
- *In an unwell child* admit for IVABs. Use Meropenem + Tobramycin + teicoplanin for 14 days as 1st line.

Id. Re-growths

- *Re-growth less than 6 months* from 1st growth - oral flucloxacillin for **4 weeks**.
- *Re-growth after more than 6 months* from 1st growth - treat as for 1st growth (see above).
- *Further re-growth within 6 months* - Two oral anti-staphylococcal antibiotics (*e.g.* rifampicin and fusidic acid) for **4 weeks**.

Ie. Chronic infection

- If there are more than 2 isolates of *S aureus* in a year, give prophylaxis with flucloxacillin as above (remember under 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), or co-trimoxazole. We may also need to use linezolid.
- Consider also skin decontamination using MRSA protocol.
- 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 **4 weeks.** This may be combined with azithromycin or clarithromycin; one further course of a cephalosporin can be given if no eradication/persistent symptoms. The sole indication for cefixime is proven *H influenzae* isolation in pure culture, with no response to first line antibiotics.

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

IIb. Re-growths

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

IIc. Chronic infection

- This is most uncommon. If $\geq$ 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 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.

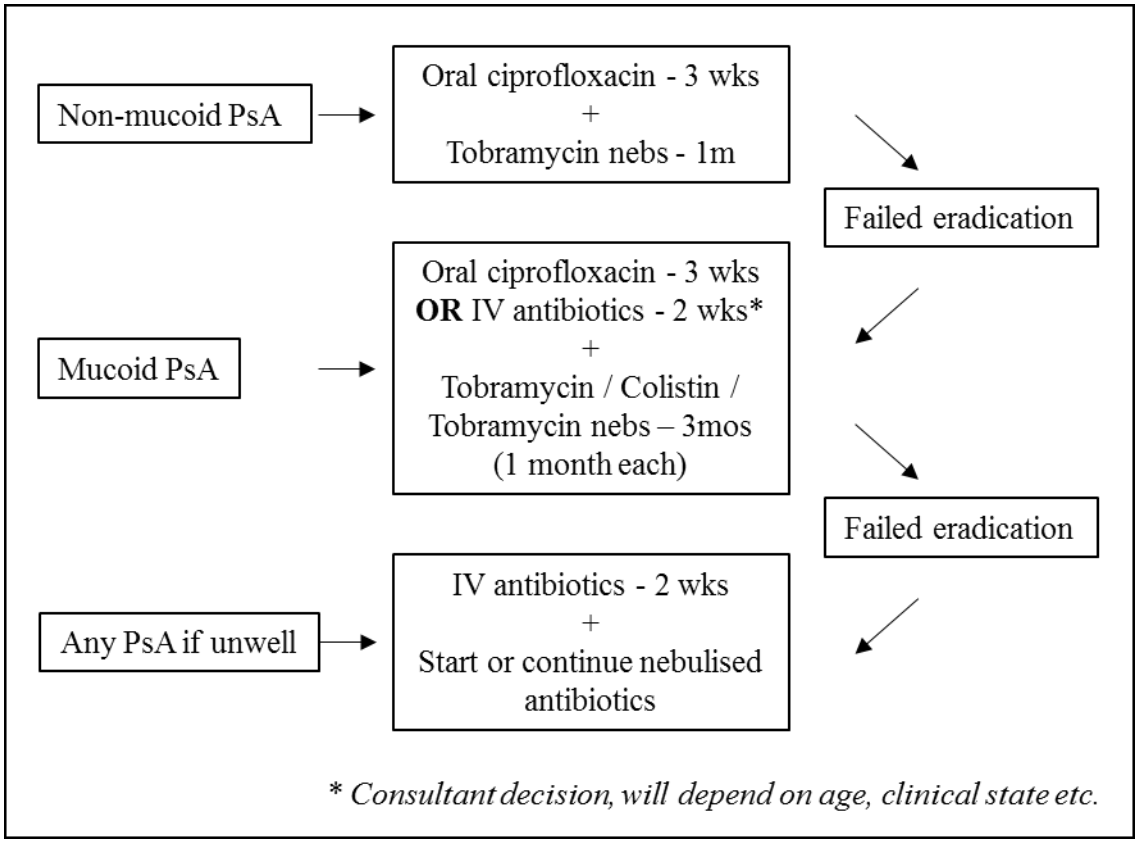
- If they remain symptomatic and sputum culture was negative, they will have an induced BAL. We will not rely on a cough swab to prove successful eradication.

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* in children 12 years and above.
- 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% (Kranzer et al, Thorax 2015).

- We use oral N-acetylcysteine at the time of IV aminoglycoside therapy for **all** courses in all children.
- There are no data on its use with nebulised amikacin and we are not using this currently.
- See formulary for doses of tablets. Children ≥12 years will have 600mg BD, and can use 600mg tablets; those <12 yrs will take 300mg BD years old (the 600mg tablets are scored and halve easily); and for children unable to take a tablet they disperse in a small amount of water.

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 on 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 on a reduced dose. This should be taken 30 minutes after the end of the infusion. Aim 20-30mg/l for tobramycin.
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.

- 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 6.15c.

- **Long term intravenous colistin**. Occasionally (although not for many years) we have used long term twice daily IV colistin for children unable to last even 3 months without 2 week courses of IV antibiotics. This is a *consultant decision*. See formulary for the dose - the usual total daily dose divided into 2 doses

IIIg. Dry powder antibiotic inhalers (see also section 6.15e).

- 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 also 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. Like nebulised antibiotics, the inhaled is excluded from the PbR tariff, so we are reimbursed if we prescribe it. 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 delivery service.

6.2a 6 IV. MRSA

- New since last guidelines: the 2018 Cochrane review included two trials with 106 CF patients with MRSA infection. In both trials the active treatment was 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. We treat for **2 weeks** with 2 oral agents - **rifampicin and co-trimoxazole.** 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 require blood levels and is the preferred choice.
- The decision to treat chronic MRSA infection is a clinical one based on signs, symptoms and investigations, and should be in accord with hospital infection policy.
- Consider using linezolid (see below), available orally and IV, when traditional agents fail (*consultant decision*).
- Check current hospital policy on the intranet; also remember surface decontamination protocols. 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 so full blood counts must be monitored weekly throughout treatment and there are reports of optic neuropathy with courses >28 days. Therefore, linezolid should only be started on consultant approval and initially we will aim for 2-week courses. For those on prolonged (4 weeks or more) or repeated courses, ophthalmological assessment is mandatory and should be repeated every TWO months. 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 a large number of species and the commonest to affect the lungs are:

This includes a large number of 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** found include *M kansasii, M xenopi, M malmoense, M fortuitum* and *M simiae*.

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 6% of all CF patients have at least one positive NTM culture in a given year (2017). 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. 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 two years after first negative sample.**

If NTM was only isolated on a BAL or IS in a non-sputum producing child, a repeat BAL or IS will be needed to stop treatment and again at a year off treatment. If possible, 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 intensive phase followed by a prolonged continuation phase (maintenance) is recommended as first line therapy. If patients do not tolerate or have side effects to any of the continuation drugs, alternative agents are suggested in Table 2. Patients on first line maintenance therapy will be regarded as 'failing' treatment or relapsing if they have the following:

- Persistent positivity on sputum AFB smear
- 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 maintenance treatment, as charted in Table 3.

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

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

A favourable response to treatment will be defined as when a patient is rendered sputum culture negative on serial samples (>4 samples) collected over a period of one year. At this point the organism will be regarded as eradicated and maintenance therapy may be stopped. A patient is considered NTM free if still clear at 12 months after completion of eradication therapy. **This is effectively two years after first negative sample.**

NEW - An ECG will be conducted to measure QT interval on those starting NTM therapy due to long term use of azithromycin, moxifloxacin, and sometimes clofazamine. If the computer readout gives a QT interval of 480ms or more, it is to be repeated and the child referred to Dr Jan Till consultant cardiologist at RBH before starting the therapies.

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 (rashes, fevers, DRESS syndrome with longer use).
- Decision of cefoxitin *vs* tigecycline is based on antibiotic sensitivities and age of the child.
- If the patient has allergies to any of first line IV drugs, add **tigecycline**. Tigecycline should be prescribed with regular anti-emetics such as ondansetron.
- Both cefoxitin and 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 and cefoxitin; this may later be swapped to oral.
- Some patients find that the continuation treatment also causes nausea and may need to continue on oral ondansetron long term. Adjustment of drug dosing schedules may help this. Second line anti-emetics are sometimes used *e.g.* aprepitant (see formulary 11.2h).
- 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) 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* + Tigecycline *IV* (12 years or over) (see below re dentition) + Ceftazidime/avibactam *IV* + 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)

- 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. If unable to tolerate tigecylcline due to vomiting the dose can be reduced to daily or alternate day dosing or 2 days out of 3.
- Begin **tigecycline** at a dose of 50mg bd; or 1.2mg/kg bd (max 50mg) for children aged 8-11 assuming dentition has been checked.

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 this is expensive (£1,100 per month), not in the national guidelines, and will require confirmation of funding from the patient's CCG via an Individual Funding Request form.

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 12 weekly 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
Rifampicin + Azithromycin + Ethambutol

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 would 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.

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.

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

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 side of the 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) side of the drug chart. They should also be drawn up and ready to administer to the patient if required. (Please refer to the latest copy of BNF-C for appropriate doses or above in allergy section).
6. If a reaction (anaphylaxis, wheezing, swelling, itching, hives) occurs during desensitisation, the procedure should be stopped and no further attempts should be made to administer that antibiotic to the patient. Please note, that some patients may feel 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 only 2% 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 it is 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 IV antibiotics

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

- The first dose of both antibiotics should always be given in hospital.

- Any Parents/Carer wishing to undertake home IV therapy must be carefully selected and be discussed with the CF Nurse Specialist and Consultant before any decision is made.

- Families must be able to follow instructions provided, be fully aware of the treatment burden and be happy to carry this out. There is a training pack and the CF nurse specialists 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 or not they are happy to do so again. In particular if there has been a long gap, consideration needs to be given to training needs (see below). Likewise, each time, an assessment will be made by the Consultant and 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 48 hours before IVs are due to start therefore prescriptions need to be in pharmacy by 12 pm at the latest. Prescription pads can be found on Rose Ward, outpatients and in pharmacy.

- Shared care doctors can fax over requests to 020 7351 8763 for the attention of the CF CNS (Mon-Fri 9.00-17.00) 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.

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

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

Site of insertion - usually via a subclavian vein into the SVC. The port is usually buried on the upper lateral chest, away from the shoulder joint and breast tissue. Ideally it should be on the non-dominant side. However, the final decision has to be left to the surgeon. If the child has had previous central neck lines, imaging of the neck (Doppler ultrasound or MR venogram) may be required to identify a suitable site for insertion.

Protocol for insertion – Consent will be taken by surgeons. Investigations: CXR, full blood count, coagulation including thrombophilia screen, U&E, group & save. If the thrombophilia screen is abnormal, discuss with Paediatric Consultant and Haematologist.

When possible, children will commence intravenous antibiotics for 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** – 4-6 weekly flushing with 3ml 0.9% sodium chloride followed by 4mls of heparinised saline (ready-made as 200 units per 2 mls). This is arranged through the CF nurse specialist with the home care team, local community paediatric nurses or local hospital. Families may eventually learn to do it.

- Local anaesthetic cream is used.
- Always use the proper needle (straight bevelled 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 Fungal disease

6.3a 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 a large number of 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 strains of Aspergillus.

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 9total IgE, Specific IgE, IgG ICAP) all sputum/BAL samples are tested for it.

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

Clinical –

- Increased wheezing/chestiness/chest tightness/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). Remember some children maintain high levels after previous ABPA.
- 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.

Oral corticosteroids: Prednisolone, given in the morning after food (not enteric coated as it is not well absorbed in CF) is normally used at a starting dose of 2mg/kg/day (max 40mg) for 2 weeks, then halve the dose for 2 weeks, review at 1 month to assess for clinical response and to plan further weaning. Only in exceptional circumstances would we use 60mg prednisolone as starting dose. We taper the dose by halving it [*e.g.* 20 mg daily goes to 10 mg daily etc.] **or** move to alternate day dosing [so if on 20 mg daily, move to 20 mg every other day, before reducing to 10 mg every other day etc.]. Reduction steps tend to occur every 2 weeks. We re-evaluate the clinical response with lung function, and total IgE, and we consider a repeat CXR. Note though that in some cases who do well, the IgE fall may lag, so treat the patient not just the IgE level.

Inhaled and nebulised corticosteroids are used by some, but not by us – there is no evidence for their use.
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, but may need to be longer depending on the response. 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.

Posaconazole –
- **1st line for treatment of ABPA in all ages.**
- **1st line for treatment of aspergillus infection/bronchitis in 8 years and above.**
- **1st line for treatment of aspergillus infection/bronchitis in 7 years and below if child unwell, or only organism cultured in a child with significant lung disease.**

It is an azole antifungal, used in combination with oral or intravenous corticosteroids. An audit carried out at RBH showed that it is better tolerated than voriconazole, and therapeutic levels are readily obtained, particularly with the tablet formulation, which should be used in preference to suspension if the patient is able to take tablets. The tablets are **not** interchangeable with liquid on a mg for mg basis. Treatment is for **6-12 weeks** depending upon therapeutic response and is stopped 2-4 weeks after the corticosteroids.

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.

Itraconazole -
- **1st line for treatment of aspergillus infection in 7 years and below if routine culture in a well child.**

Give orally (monitor liver function) and continue whilst they remain on steroids. We use posaconazole in a younger child with aspergillus infection if the child is unwell or respiratory concerns and this is all that is cultured.

The liquid preparation should always be prescribed on an empty stomach. Stop ranitidine/PPIs if possible to improve absorption. The capsules are poorly absorbed and are a last resort (as the liquid has a poor taste so may be refused), they must be taken with acidic drinks (*e.g.* Coca-Cola, orange juice, but not grapefruit juice), but **with** food.

Itraconazole is stopped 2-4 weeks after the oral steroids are finished, although some children with recurrent ABPA stay on it for longer.

NB. Itraconazole should also be given to anyone taking oral steroids (for whatever reason) if there is any suggestion of concomitant aspergillus infection while they are taking the steroids.
Itraconazole levels

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

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 or itraconazole 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 small risk of raised blood glucose.

Beware of drug interactions *e.g.* with rifampicin, ivacaftor, Orkambi; and if azoles given with inhaled corticosteroids 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/itraconazole 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 6.4 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 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 on the basis of 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.

Post script - 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 sun screen). 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 does not grow from cough swabs. It may be found in routine sputum; the significance of this in an asymptomatic child with normal ABPA blood markers is unclear, and whether to treat is a case by case decision. If grown on a BAL or induced sputum (done for clinical concern) we will always try to eradicate it with a one month course of oral liquid itraconazole if aged <8 years, or oral posaconazole if 8 years and above.

- **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 use one month course of oral liquid itraconazole if aged <8 years, or oral posaconazole if 8 years and above.

- **Invasive disease** is rare but may occur in severely debilitated, immunosuppressed (including steroids) 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 rarely seen in CF but has been described. Suspect if halo sign in a cavity and 6-8 positive IgG ICAP. Confirm with CT. Treatment individualised - too rare to offer guidelines.

- **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.

6.3b Scedosporium apiospermum & Lomentospora prolificans

Scedosporium is the second commonest fungus isolated in CF respiratory secretions; *Lomentospora prolificans* has been renamed recently from *Scedosporium prolificans*, 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.

If treatment is considered, check sensitivities –
Scedosporium apiospermum – we will use **posaconazole + terbinafine** 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.

6.3c 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.

6.3d 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.

6.4 Corticosteroids

Indications for oral steroids:

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

We tend to use prednisolone which must **not** be enteric–coated otherwise absorption is poor in CF. Dexamethasone may also be used and anecdotally may be better for those whose behaviour/mood is adversely affected by prednisolone (NB *prednisolone 5 mg = dexamethasone 0.75 mg*). Dose regimen for ABPA is in section 6.3. 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 compliance with oral prednisolone is an issue.

Attention must be paid to potential adverse effects, particularly glucose intolerance as sometimes overt CF-related diabetes is precipitated. Patients must be told to report polyuria & 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). If a child is on long term oral steroids itraconazole will usually be given in case there is exposure to aspergillus.

Indications for inhaled steroids

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

We use budesonide or fluticasone, 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) are most suitable. High doses of inhaled steroids are preferably given via a spacer device to reduce mouth deposition and potential systemic side effects. However, there will be some older children for whom a spacer is unacceptable and then a DPI should be used. Use of a standard metered dose inhaler alone must be actively discouraged.

Side effects may include a reduction in final height (long term asthma studies suggest 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) in a combination inhaler (Seretide or Symbicort). The patient must never take the LABA alone (without an inhaled steroid) so we do not prescribe salmeterol or formoterol inhalers.

6.5 RhDNase (Dornase alfa, Pulmozyme)

Note that Dornase alfa is drug name and how it appears in BNFc and Medchart®. Pulmozyme is trade name. However, since all families call it DNase we continue to use that name.

RhDNase 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 rhDNase in children less than 6 years old.

- Our policy is to consider starting rhDNase for **ALL PATIENTS WHEN THEY ARE 6 YEARS OLD, whatever their lung function** (as per European CF Society

recommendations). Our intention is that it would be for unusual for a child aged 6 and above not be commenced on it.

- For our current older patients, its use needs to be discussed. We would strongly suggest we start any child
    - whose FEV_1 is <85%.
    - who hardly expectorates at all but has symptoms.
    - who has persistent wheezing.
- We would consider it in preschool children if there is concern over their respiratory status (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.
- We still offer it to well 6 year olds on ivacaftor, although data are lacking.

Other indications include.

- Persistent or recurrent focal x-ray changes *e.g.* consolidation in a lobe or segment, when we would consider bronchoscopy with instillation under direct vision – see section 6.14. It would be expected a child like this would already be on rhDNase 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 rhDNase use as a proxy for reduced inflammation.

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

6.6 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 rhDNase (section 6.5) and as a cheaper alternative. However, studies show that some patients respond better to rhDNase and others to HS so a trial of therapy is important. We commonly use HS once a day in the morning immediately pre-physiotherapy and rhDNase 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) 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. We think it likely that the hypertonic saline could be administered at the time of Infant PEP physiotherapy in the infant age group but at the time of writing, this has not yet been tried. For now, we will target patients we feel are most likely to benefit, *e.g.* those taking lots of oral antibiotics, those with more respiratory symptoms etc. We will then review this policy in a year or so and decide whether it is appropriate to offer this routinely to all newly diagnosed infants with CF.

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 before **every** dose and spirometry **must** be performed before **and** after the first dose in hospital prior to home therapy. Occasional patients have to 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% H/S at this stage. In children too young for spirometry, we monitor oxygen saturation with auscultation for the 1st dose.

Dose: 4mls 7% HS once or twice a day via nebuliser just before physiotherapy. We use 7% 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 have to 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 rhDNase) may be combined with an airway clearance device when there are particular adherence issues: 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

6.7 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 (appendix 16).
https://www.england.nhs.uk/wp-content/uploads/2017/03/commissioning-medicines-children-specialised-services.pdf

Mannitol should be considered third line (after DNase and HS) in those who do not respond to DNase 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 DNase, 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.

6.8 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: Very similar to those for rhDNase (see section 6.5) and should include those not benefiting from a 3 month trial of rhDNase.

Dosage: 250 mg once daily (<40kg) or 500 mg once daily (≥40kg) **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 abnormalities and reversible tinnitus although only one transient LFT abnormality was observed during our study. Liver function tests should be performed at any time blood is being taken for other reasons and at annual assessment.

One study found symptom free, **small** increases in QTc interval from normal to borderline in 4 adolescent males but no children. Use of azithromycin **and** erythromycin (prokinetic) long term should be avoided due to potential additive side effects. We are now conducting an ECG on all patients starting long term azithromycin (and those already on it). If the computer readout gives a QT interval of 480ms or more, it is to be repeated and the child referred to Dr Jan Till consultant cardiologist at RBH.

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.

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.

6.9 CFTR modulators

6.9a Ivacaftor

In 2012, ivacaftor was approved by NHS England for clinical use in CF patients 6 years of age and above with at least one copy of the G551D mutation. All eligible patients in our clinic were commenced on this oral preparation, which is planned for long-term, uninterrupted use. The drug has since been approved for the other known gating mutations (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D). Funding for the granule formulation was agreed in Dec 2016 for children aged 2-5 years, and since December 2019 for those aged 6 months and above, with the same group of mutations. We should prepare for starting treatment soon after diagnosis. Since October 2019, 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), nor those with 9T.

Ivacaftor (Kalydeco) is a small molecule drug which binds to CF at the cell surface and leads the chloride channel to open (this is termed 'potentiation'). Class 3, the 'gating' mutations lead to channels which are not open often enough; the commonest of these is G551D. Phase 3 trials demonstrated significant improvements in FEV_1 (around 16-17% relative to baseline), reduction in exacerbations, significant weight gain, and a large drop in sweat chloride (often into the borderline, or even normal, range) in G551D and the other gating mutations. Trials have confirmed more modest efficacy in adults with the class 4 (conductance) mutation R117H, but efficacy was not evident in younger children for whom the drug is not licensed in Europe.

Ivacaftor is administered twice daily and it is crucial that it is 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

- Were minimal in trials, although rashes are common.
- Rises in liver function tests were observed in some patients, and although these did not differ significantly from the placebo group, monitoring has been put in place (see below). This was seen more commonly in the 2-5 yr old age group and was more common in children with previously raised LFTs. Encouragingly, trials in younger children 6-24 months old have not shown any further increase in this occurrence. Dose reduction recommendations are available for patients with *significant* hepatic or renal impairment.
- The finding of cataracts in neonatal rats exposed to high doses of the drug 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 12 years) are recommended in paediatric patients initiating ivacaftor treatment.

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

- **Azole antibiotics**: (itraconazole, voriconazole, posaconazole) lead to inhibition of the breakdown pathways of ivacaftor and accumulation of the drug. If co-administration is necessary, the dose of ivacaftor should be reduced; manufacturers suggest to twice

weekly although this comes from modelled data, not human PK studies, and anecdotally, this may lead to loss of efficacy. Consultant advice should be sought in this event. Ivacaftor levels are not currently available but sweat Cl^- could provide a useful surrogate for bioavailability.

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

Pre and on-treatment monitoring & stopping criteria.
Due to the very high cost of the drug, the Commissioners in England have mandated monitoring and have imposed stopping criteria. See www.england.nhs.uk/wp-content/uploads/2013/04/a01-p-b.pdf .

- **Sweat test** should be done within the 6 months prior to starting treatment and again at the next routine appointment (around 8 weeks). It is repeated annually.

The patients will be considered to have responded to treatment if either

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

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

a) the patient's sweat chloride test falls by at least 30% **OR**
b) the patient demonstrates a sustained absolute improvement in FEV_1 of at least 5%. In this instance FEV_1 will be compared with the baseline pre-treatment level one month and three months after starting treatment. Obviously, this does not apply to 2-5 year olds.

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

- **Liver function** tests needs performing every 3 months for the first year but can then be done with annual assessment.
- **Stool elastase** in 2-5 yr olds before starting then at 6 months. Consider at intervals thereafter based on symptoms and creon requirement. Restoration of pancreatic exocrine function has been seen in a proportion of young children and less frequently even in older patients.

- **Ophthalmology examination** before starting, repeat after 1 year, then annually in under 18 yr olds.

6.9b Orkambi

The commonest CF mutation, F508del, results in CFTR protein which does not reach the cell surface and it has clearly been shown that ivacaftor, as a single agent, is ineffective in people homozygous for this mutation. Although efficacy was confirmed when ivacaftor was used in combination with the corrector molecule, lumacaftor (Orkambi), funding through NHSE was initially declined on the basis of lack of cost effectiveness after evaluation by NICE (https://www.nice.org.uk/guidance/indevelopment/gid-tag530).

However since October 2019, NHSE have agreed to it being prescribed to children above 2 years with **homozygous Phe508del variants**. In practice it will be used for 2-11 year olds, as those aged 12 and above can receive Symkevi, which has a better safety profile.

The Vertex Managed Access Programme for those with severe lung disease is no longer in place.

Based on well-described early adverse respiratory effects which were more common in the more severely unwell patients, we commence treatment in hospital (2-3 day stay) and at half the recommended dose for 24 hours for those with severe lung disease or those with significant obstructive airways disease. This included all those previously on the MAP. However, when starting 2-11 year olds, most of whom are well, this is not necessary. It is a consultant decision if the child can be started at home. The parents are also counselled by one of our pharmacists.

The medication will be delivered to the homes by a home delivery service (currently Healthcare at Home or Lloyd's Pharmacy).

Monitoring
We will comply with NICE data collection details. We can start drugs before this is finalised.

- **Eyes** – we will ask all patient to have this checked, at baseline and repeat yearly. SPCs say 'paediatric' patients at baseline and follow up – no more details. 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).
- **Liver function** – Baseline or use results if taken within 3 months. Repeat 3 monthly for 1 year then at annual review.
- **Lung function –** standard spirometry.
- **Blood pressure** – ensure measured in clinic.
- **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.
- **Faecal elastase** – at 6-12 months. No need for baseline.

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. There are too many patients to compile a separate database.

6.9c Symkevi

The second dual combination (tezacaftor/ ivacaftor) demonstrated similar efficacy to Orkambi but improved tolerability. It also has fewer drug-drug interactions and does not cause respiratory symptoms when starting so patients can all be started at home.

Since October 2019, NHSE have agreed to it being prescribed for those aged 12 years and above. Once it is licensed for younger age groups, we will be able to use it on those children instead of Orkambi.

Eligible genotypes –

- Phe508del homozygous
- Phe508del heterozygous with P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H*, 2789+5G→A, 3272 26A→G, and 3849+10kbC→T.

  *D1152H may be a CFSPID patient so we may feel not indicated without CF disease, although it is one of the licensed indications.

Laboratory source document of genotype must be consulted (and given to parents). Make sure that alternate names are checked as some of the rarer ones eligible for Symkevi have a number of names.

Monitoring

Exactly the same as for Orkambi (see section 6.9b).

6.9d Triple therapy (Trikafta)

Trikafta consists of Ivacaftor, Tezacaftor and Elexacaftor (Triple therapy). The phase 3 studies are now published (Nov 2019). Results are very positive (in the same range as Ivacaftor effect in gating mutations), for those with:

- Phe508del homozygous.
- Phe508del heterozygous with Minimal Function variant.

FDA licensed the drug in November 2019, EMA decision is awaited. Once licensed it will need to be evaluated by NICE before a decision can be made by NHSE.

There is a Managed Access Programme run by Vertex for those with very severe lung disease.

Any child receiving CFTR modulator drugs as part of a clinical trial will have these tests performed as per the trial protocol and does not need them performing in the clinic unless there is a clinical concern. Please contact Jane Davies with any queries. The trials team will inform the clinical team via EPR / e-mail when investigations have been performed and whether there is any clinical concern over these (although some results may not be available, *e.g.* sweat Cl^-).

6.10 Haemoptysis

Streaky haemoptysis is common with chronic infection but may indicate deterioration so sputum should be cultured and a course of antibiotics considered. Haemoptysis must be differentiated from 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 DNase 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.

Positioning

- 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.

NIV

- 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 DNase. • 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	• Urgent medical review. • Position patient with bleeding lung down.

> 250mls blood in 24 hours	• 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; dose (from BNFc) is 2mg then 2mg every 4 hours until bleeding is controlled, (maximum duration 48 hours); this is used by the adult unit.
- **Bronchoscopy** - It is rarely useful in the acutely bleeding child. If you are considering this procedure initially try flexible, then consider a rigid, under general anaesthetic. With massive haemoptysis, go straight to rigid bronchoscopy. This can be technically very difficult but may allow clot removal (beware precipitating further bleeding), tamponade of bleeding site using a Fogarty catheter, or haemostasis with thrombin glue or iced saline lavage/vasoconstrictor lavage.
- **Selective bronchial angiography and embolisation** can only be carried out by experienced specialists in a tertiary centre. Numerous dilated tortuous bronchial arteries are often identified some of which may take origin from aberrant sources. Actual source of bleeding is difficult to discern but generally a number of large vessels (>2.5mm) are embolised using variable sized gel foam pledgets. Great care to avoid spinal artery (with consequent paraplegia) and other systemic artery embolisation is necessary. Post embolisation pain requiring narcotic analgesia and transient dysphagia are common. This is not a cure and many patients develop new vessels within months or years that may bleed and so require further embolisation.
- **Oral tranexamic acid** has been used long term in recurrent bleeders with some success. 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.

6.11 Pneumothorax

Please contact us. A high index of suspicion is needed - consider the diagnosis if there is unexpected deterioration, unexplained chest pain, or worsening breathlessness. If in doubt, do

a CXR but CT scan may be needed to detect it or determine optimal site for drain placement. The incidence of pneumothorax increases with age (overall 8%) and is a marker of severe lung disease. It carries a bad prognosis, particularly if the chest drain cannot be rapidly removed. All but the most trivial pneumothorax in a stable patient mandates admission to hospital.

A tension pneumothorax is an emergency that requires urgent treatment with a 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.
- 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 6.17.
- 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.

6.12 Intractable wheezing / severe small airways disease

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

In contrast, the foregoing discusses a small (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?
- Is there an obvious clinical atopic history (not just skin testing) for example animals, HDM etc?

If these all negative:

- Consider CT scan to assess structural damage / bronchiectasis (including expiratory views).
- Consider bronchoscopy and pH study.
- Consider 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 really 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.
  One 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 increasing evidence that steroids (oral and inhaled) increase the risk of isolating NTM so as always, a consideration of risks and benefits is required. Consider small molecule ciclesonide.
- Consider **Tiotropium inhaler** – an antimuscarinic agent. Although only licensed >18 years it may still be necessary for this difficult problem in younger patients. This is a *Consultant decision*. We should use the Spiriva Handihaler (dry powder) 18 mcg once daily. We do not use the Spiriva Respimat MDI as the product license specifically states not to be used in CF due to potential increase in adverse events/exacerbations; however there have been two recent 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 theophyllines *e.g.* Slophyllin – see BNFc for doses.
- Consider also IV aminophylline for an in-patient with severe wheezing (use standard acute asthma doses).
- Consider a trial of Montelukast.

If above fails after 2-4 weeks:

- **Prednisolone** 2mg/kg/day in the morning for 14-21 days then review. If successful, then try to wean over two weeks to 1mg/kg alternate days.
- **Pulsed methylprednisolone** can also be considered 10mg/kg once a day (maximum 1 gm/day) for 3 days (3 doses in total) and this can be repeated as a single dose weekly in severe, intractable cases. This is given as an infusion over 30 mins, there is a risk of heart failure if given as a bolus.

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

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

  As part of the DoH Demand Management Plan, we are now required to obtain confirmation of funding from the patient's CCG **before** initiating treatment. It is also mandatory for outcome data to be collected to ensure reimbursement. For CF this is improvement in FEV_1; improved exercise tolerance and reduction in days of school. Where IV immunoglobulin therapy is being considered contact the pharmacy team as soon as possible, as this process can take weeks. See trust guideline on the intranet.

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

- **Azithromycin.** No objective evidence in this situation but 250mg/day if <40kg or 500mg/day if >40kg given daily for six months may be beneficial although the effect may take at least 2 months to be seen. We are now conducting an ECG on all patients starting long term azithromycin (and those already on it). If the computer readout gives a QT interval of 480ms or more, it is to be repeated and the child referred to Dr Jan Till consultant cardiologist at RBH before starting AZM.

6.13 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.

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, 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, social worker, safeguarding team.

In these circumstances, the CF Focus meeting will decide if further investigations are necessary (*e.g.* bronchoscopy, CT scan, pH study, CGMS), any referrals to be made (*e.g.* gastroenterology, clinical psychology, safeguarding), and a treatment plan.

We will also do a **formal review of adherence** –
- Prescription uptake from GP and hospital (RBH & local) pharmacy.
- Downloading data from nebulisers when possible.

- Home visit to assess medications.
- Blood levels if relevant *e.g*. prednisolone, posaconazole.
- When an in-patient, SAM scheme (section 4.5) assessment.

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).

6.14 Bronchoscopy

Indications in CF:

1. Need for **microbiological diagnosis** in a non-sputum producing child:

- Not responding to IV antibiotics.
- Not previously infected with *P aeruginosa* in whom there is clinical concern due to persistent deterioration (do not simply start empirical antipseudomonal therapy).
- 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 6.15f), and this practice has meant we need to do fewer bronchoscopies, certainly in older children. Arrange with the physiotherapy dept.

2. **Therapeutic suctioning**:

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

3. **Other indications**:

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

Bronchoscopies are performed on Monday or Friday afternoons in Theatres, booking for in-patients is done through bed managers. Bookings for out-patients who are to be admitted are through the Bed Manager (ext. 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 is often done at the start of a 14 day IVAB course when the patient is not doing well, and no microbiology is available, or nothing is ever grown. 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 rhDNase may be instilled down the bronchoscope suction channel to a localised collapsed area that is obstructed by thick mucus. The dose is 2.5 mg in 10 mls 0.9% sodium chloride, and then a small amount of air is instilled down the bronchoscope to ensure no drug is left in the suction channel. If the rhDNase 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).

6.15 Chest physiotherapy

6.15a Exercise

The importance of exercise is highlighted as evidence links exercise capacity to improved survival, and therefore exercise should be incorporated in the patient's life from an early age. Exercise has been shown to reduce sputum viscosity, improve ventilation and peak expiratory flow, and facilitate movement of mucus. Exercise prior to airway clearance has been shown to have an additive effect on sputum expectoration but must be combined with Forced Expiratory Technique (huffing, coughing, breathing control) to clear sputum effectively. Exercise needs to be consistent and varied and fit into family life with the aim of it becoming a family habit. Web based logs and digital software may be useful in motivating certain age groups.

6.15b Airway Clearance Techniques

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

- **Babies and infants**– Techniques taught may include modified gravity assisted positioning (this is NOT tipping) and intermittent chest clapping; as well as infant positive expiratory pressure (PEP), assisted autogenic drainage (AAD) and age appropriate exercise.
- **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.
- **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 8 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, 3rd edition April 2017. Also see the following link for patient information leaflets on individual techniques: https://www.cysticfibrosis.org.uk/the-work-we-do/clinical-care/supporting-clinicians/resources-for-clinicians/physiotherapy-leaflets.

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

Other physiotherapy issues that may be discussed are:

- **Musculoskeletal issues and posture** – Screened at annual assessment; education and onward referral is provided as required.
- **Urinary incontinence** – Stress incontinence can occur even in young children during activities such as coughing, laughing and exercise. The patient can be taught pelvic floor exercises and a technique known as 'the knack' (a pelvic floor contraction). Please consult the physiotherapist for advice (further information in section 8.9).
- Upper airway treatment via nasal douching or sinus nebulisation may also be taught where appropriate. Please see ENT section 8.5b for more information

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.

6.15c. Inhaled Drug Response Assessment (bronchoconstrictor challenge)

See appendix 6 for details of Drug Response Assessment and pass/fail criteria.

For inhaled antibiotics (nebulised and dry powder) and hypertonic saline the child must always have a drug response assessment to detect any bronchoconstriction when the 1st dose is given. This should be done in hospital and requires the patient to perform pre and post dose spirometry. If the patient already 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 at a later date 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.

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

6.15d 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 Philips Respironics directly (08001300857) 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 rhDNase 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 - rhDNase (1ml fill volume)

Lilac latched chamber - Tobi, Bramitob, Tymbrineb and hypertonic saline. As the chamber takes a max of 2.5 mls, the dose has to 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 7).

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 **(Fungizone)**	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.	no	no	yes**	yes	post
(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
rhDNase	n/a	yes- **green**	yes	Yes*	no	>30 minutes pre ACT or on discussion with the physiotherapist

DRUG	Mixed with	Device			Exhaust Filter	Timing with ACT
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 125mg = 2.5mls 250mg = 5mls	no	no	Yes**	yes	post
Tobramycin - Bramitob	n/a	yes lilac x 2 fills per dose	Yes (but not recommended in <5yrs)	yes**	yes	post
Tobramycin - TOBI or Tymbrineb	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 (take into account 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 8 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.

6.15e 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 6.15c), and to learn how to use the device.

Each dose of tobramycin inhalation powder is made up of 4 capsules. These are stored in blister packs clearly marked for morning and evening use. Doses are ideally taken 12 hours apart, but definitely not closer than 6 hours apart. As with most inhaled antibiotics it is recommended they are taken after 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 6.15c), 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.

6.15f Induced sputum (IS)

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.

An appointment for sputum induction takes approximately 1 hour. It involves the child inhaling 7% hypertonic saline for 15 minutes via an ultrasonic nebuliser device. A cough swab is taken, and a bronchodilator is administered prior to the test. In children over 5 years of age spirometry is performed to establish post-bronchodilator lung function. Spirometry is repeated at 5 minute intervals during the nebulisation to assess for bronchoconstriction. At these 5 minute intervals the child will be asked to huff and cough or will be guided to carry out airway clearance techniques to expectorate secretions. 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.

6.16 Oxygen

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

If saturations were low and oxygen was required at the start of the admission, then the overnight monitoring should be repeated at the end of the admission. If they remain low (**saturations <90% for >5% of the time**), then consideration should be given to providing oxygen at home, almost always only at night. When home oxygen is initiated, an overnight transcutaneous CO_2 should also be recorded, as it can rise slightly when oxygen therapy is initiated. As this is for >8 hours then an oxygen concentrator is preferred to cylinders.

Oxygen prescription submission is managed by the RBH oxygen service. Their contact details are oxygen@rbht.nhs.uk or bleep 7755 or ext. 84451. When prescribing oxygen, 2 forms should be completed for each patient and sent to the RBH oxygen service, namely, the Brompton Domiciliary Oxygen Referral Form and the IHORM (v.9 - January 2017) + new HOCF (October 2016). 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/ The RBH oxygen service will then send a HOOF Part B form to the relevant NHS oxygen supply company. For the record, the current suppliers are Air Liquide (London, North West, East Midlands, South West); Baywater Healthcare (Yorkshire & Humberside, West Midlands, Wales); BOC (East of England, North East); Dolby Vivisol (South East, South Central, Scotland).

6.17 Non-Invasive Positive Pressure Ventilation (NIPPV)

NIPPV has a number of uses:

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

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