12 MEDICINES FORMULARY

13.1: Oral Antibiotics

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Chloramphenicol	<u>Treatment</u> 12.5 – 25 mg/kg QDS. Usually 500 mg QDS; maximum 1g QDS. May be prescribed at higher dose initially and reduced to lower dose as soon as clinically indicated, e.g. 1g QDS for 24-48h, reducing to 500mg QDS thereafter	*H. influenza;* Anecdotal reports of a clinical response in patients with *P.aeruginosa* and *B.cepacia* complex. The patient should be fully informed of the risks of chloramphenicol: blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia), peripheral neuritis and optic neuritis. There are no reported cases of aplastic anaemia in a CF patient but this does not warrant complacency. Needs full blood count at day 21 if course longer than 3 weeks. Courses not normally repeated within 3 months.	**Hepatic effects** Avoid if possible in hepatic impairment. If not possible, reduced dose may be required to maintain trough level <10mg/L. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function Manufacturers recommend monitoring levels in patients with renal impairment. Therapeutic range: peak = 10-20 mg/L; trough = 5-10 mg/L	**Pregnancy** Not associated with increased incidence of congenital malformations. Concerns that use near term may be associated with a risk of neonatal Gray Baby Syndrome are not supported by evidence. **Lactation** An alternate drug is preferred to chloramphenicol during breastfeeding, especially while nursing a newborn or preterm infant. If the mother must receive chloramphenicol during nursing, monitor the infant for gastrointestinal disturbances and adequacy of nursing. Monitoring of the infant's complete blood count and differential is advisable. In some cases, discontinuation of breastfeeding might be preferred.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ciprofloxacin	<u>Treatment</u> 750mg BD	*P. aeruginosa* Included in RBH NTM protocol Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping. Quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use; patients over 60 years of age are more prone to tendon damage; the risk of tendon damage is increased by the concomitant use of corticosteroids; if tendinitis is suspected, the quinolone should be discontinued immediately. Patients should be reminded about photosensitivity - avoid exposure to sunlight or UV radiation and use high factor sun block during and for up to 4 weeks post treatment. Dairy products will reduce absorption. Avoid for at least 30 min. before and after taking ciprofloxacin. May lower seizure threshold - use with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued.	**Hepatic effects** No dose adjustments necessary in hepatic impairment. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Reduce to 50% of normal dose (100% of dose may be used for short periods in exceptional circumstances – seek advice from a pharmacist).	**Pregnancy** Limited evidence does not suggest any increased risk of adverse pregnancy outcomes. **Lactation** Fluoroquinolones have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, recent studies indicate little risk. The calcium in milk might prevent absorption of the small amounts of fluoroquinolones in milk, but insufficient data exist to prove or disprove this.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Clarithromycin	Treatment 500 mg BD Extended release 1000mg OD may be required in some circumstances.	*S. aureus*; *H. influenzae*; mycoplasma Included in RBH NTM protocol. Interacts with some drugs metabolised by CYP450 isoenzyme system – may increase plasma concentrations of drugs such as theophylline, ciclosporin, tacrolimus, simvastatin, warfarin. Contact pharmacist for further advice.	**Hepatic effects** Use with caution in hepatic impairment. **Renal Impairment** **GFR >30mL/min** Dose as in normal renal function **GFR <30mL/min** 250-500mg BD (<10mL/min, vomiting may be a problem with higher doses). Avoid extended release preparations in severe renal impairment.	**Pregnancy** Exposure to clarithromycin during pregnancy has not been associated with teratogenic effects. **Lactation** Because of the low levels of clarithromycin in breast milk and administration directly to infants, it is acceptable in nursing mothers. The small amounts in milk are unlikely to cause adverse effects in the infant. Monitor the infant for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis.
Co-amoxiclav (amoxicillin + clauvulanic acid)	Treatment 625 mg TDS	*S. aureus;* *H. influenzae (β-lactamase positive);* *Moraxella catarrhalis* Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. The risk of acute liver toxicity is reported to be about 6 times greater with co-amoxiclav than with amoxicillin. Cholestatic jaundice is more common in patients above the age of 65 years and in men. Jaundice is usually self-limiting and very rarely fatal.	**Hepatic effects** Use with caution and monitor liver function at regular intervals (use with caution in CF liver disease). Due to clavulanic acid content duration should not exceed 14 days without review. Contra-indicated if patient has previous history of jaundice/hepatic dysfunction which may be penicillin associated. **Renal impairment** **(all levels)** Dose as in normal renal function.	**Pregnancy** No conclusive evidence of an increased risk of congenital malformations or foetal loss following maternal exposure to therapeutic doses. **Lactation** Amoxicillin and clavulanic acid is acceptable to use during breastfeeding. Limited information indicates that serious reactions in infants are very uncommon during the use of amoxicillin-clavulanic acid during nursing.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Co-trimoxazole (sulfamethoxazole and trimethoprim)	<u>Treatment</u> 960 mg BD <u>Prophylaxis</u> 960 mg BD	Used mainly for *S maltophilia*. Also active against *S. aureus*, *H. influenzae* and may be useful for *B. cepacia*. Included in RBH NTM protocol Associated with rare but serious side effects: Stevens-Johnson syndrome, bone marrow suppression and agranulocytosis. Monitor FBC in prolonged courses. Advise patient to report sore throats and fevers. Stop if rash or blood disorder develops.	**Hepatic effects** No data are available relating to dosage in patients with impaired hepatic function. Contra-indicated in patients showing marked liver parenchymal damage. **Renal Impairment** **GFR 30-50mL/min** Dose as in normal renal function **GFR <30mL/min** 50% of normal dose	**Pregnancy** Avoid in pregnancy: Potential increased risk of hyperbilirubinaemia in neonates with other risk factors. **Lactation** With healthy, full-term infants it appears acceptable to use sulfamethoxazole and trimethoprim during breastfeeding after the newborn period.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Doxycycline	<u>Treatment</u> 200mg on first day then 100-200 mg OD <u>Prophylaxis</u> 100mg daily	Can be useful for *S maltophilia* and *B cepacia*, and MRSA. Also active against most *H. influenzae* and some *S.* aureus Included in RBH NTM protocol Advise patients to swallow caps/tabs whole, with plenty of water and in an upright position to avoid oesophageal irritation. Headaches and visual disturbances need investigating (benign intracranial hypertension reported with tetracyclines). Discontinue if blood disorders develop. Patients should be reminded about photosensitivity - avoid exposure to sunlight or UV radiation and use high factor sun block during and for up to 4 weeks post treatment.	**Hepatic effects** Avoid or use with caution in patients with hepatic impairment or those receiving potentially hepatotoxic drugs. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Use in pregnancy is associated with perturbed fetal bone growth, congenital cataracts and discolouration of teeth in the child and may exacerbate fatty liver of pregnancy in the mother. Tetracyclines should be avoided after the first trimester unless compellingly indicated. **Lactation** There is not likely to be harm in short-term use of doxycycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breastmilk. Short-term use of doxycycline is acceptable in nursing mothers. As a theoretical precaution, avoid prolonged or repeat courses during nursing. Monitor the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhea or candidiasis

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ethambutol	<u>Treatment</u> 15mg/kg (maximum 1.5g) OD (round dose to nearest 100mg)	Included in RBH NTM protocol – *M.avium* complex. Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. Test visual acuity with Snellen chart, and colour vision with Ishiharhi colour vision test before treatment and warn patient to report visual changes.	**Hepatic effects** No dose adjustment required in hepatic impairment **Renal Impairment** **GFR 10-50mL/min** Dose as in normal renal function **GFR <10mL/min** 15mg/kg every 48h or 7.5mg/kg/day	**Pregnancy** The literature supports the safety of ethambutol during pregnancy. **Lactation** Limited information indicates that maternal doses of ethambutol up to 15 mg/kg daily produce low levels in milk and would not be expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months.
Flucloxacillin	<u>Treatment</u> 1 – 2g QDS <u>Prophylaxis</u> 1g BD (can increase to 2g BD)	*S. aureus* Patients should be advised to take 1 hour before meals or on an empty stomach as far as practical. Review at discharge whether to resume on prophylactic dose. Cholestatic jaundice and hepatitis may occur very rarely, up to two months after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors.	**Hepatic effects** Cholestatic jaundice, hepatitis and reversible changes in LFT's are rare and may occur up to 2 months after treatment has been stopped (more common following prolonged therapy). Contraindicated in patients who have a history of flucloxacillin associated hepatic dysfunction or jaundice. Use with caution in patients with hepatic dysfunction. In prolonged treatments regular monitoring of hepatic function is recommended. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Considerable clinical experience has not indicated adverse foetal effects when flucloxacillin is used in pregnancy. **Lactation** Penicillins and cephalosporins are the antibiotics of choice during breastfeeding. However, trace quantities of flucloxacillin can be detected in breast milk: the possibility of hypersensitivity reactions must be considered in breast-feeding infants.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Fusidic acid/ sodium fusidate	<u>Treatment</u> sodium fusidate tabs 500mg TDS; fusidic acid liquid 750mg TDS (Doses may be doubled in severe infection) NB Doses of fusidic acid are higher than sodium fusidate due to differences in bioavailability (fusidic acid is incompletely absorbed). Fusidic acid 375 mg **≡** sodium fusidate 250 mg.	*S. aureus* Patients should be advised to take with or after food Should always be prescribed with additional anti-staphylococcal agent to prevent resistance.	**Hepatic effects** Periodic LFTs recommended if on high dose, prolonged therapy or in patients with liver dysfunction. Caution when taken with other antibiotics with similar biliary excretion pathways (rifampicin). It displaces bilirubin from its albumin binding site *in vitro*. The clinical significance of this finding is uncertain. Drug elimination may be decreased in hepatic impairment, biliary disease and biliary obstruction; avoid or reduce dose. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Inadequate evidence of safety in human pregnancy. **Lactation** Safety in nursing mothers has not been established. When sodium fusidate has been given systemically, levels have been detected in the breast milk. Caution is therefore required when used in mothers who wish to breast feed.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Linezolid	<u>Treatment</u> 600 mg BD	Last line for MRSA or *S aureus* where patients have not responded to conventional agents e.g. high dose flucloxacillin, rifampicin, fusidic acid. Courses >28 days (consultant decision only) leads to risk of optic neuropathy. Patients should be warned to immediately report any visual changes, regardless of treatment duration. Patients expected to need >28 day course or repeated courses should have ophthalmic exam before starting first course and every 2 months after. Haematopoietic disorders reported – full blood counts should be monitored weekly. Close monitoring needed if treatment for more than 10–14 days, pre-existing myelosuppression, severe renal impairment or receiving any drugs that may affect haemoglobin, blood counts or platelet function. Linezolid is a reversible monoamine oxidase inhibitor and therefore should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B, or within two weeks of taking any such medicinal product.	**Hepatic effects** No dose adjustment is required in hepatic impairment, however, in severe hepatic impairment use only if potential benefit outweighs risk. **Renal Impairment** **(all levels)** Dose as in normal renal function. Monitor closely if GFR <10mL/min: if platelet count drops on dose of 600mg BD, consider reducing to OD.	**Pregnancy** No reports of use during human pregnancy: use alternatives if possible. If no other alternatives are available and linezolid must be used, the maternal benefit appears to outweigh the unknown foetal risk. **Lactation** If linezolid is required by the mother, it is not a reason to discontinue breastfeeding. Monitor the infant for possible effects on the gastrointestinal tract, such as diarrhoea, vomiting, and candidiasis. However, because there is no published experience with linezolid during breastfeeding, an alternate drug may be preferred, especially while nursing a newborn or preterm infant.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Metronidazole	<u>Treatment</u> 400 mg TDS	most anaerobic protozoa; Gram-negative anaerobes Remind patients to avoid alcohol for duration of therapy. May darken urine. Do not use suspension in patients taking ranitidine or PPIs due to limited absorption – if tablets cannot be swallowed whole, crush and disperse in water.	**Hepatic effects** Significant accumulation may occur in patients with hepatic encephalopathy resulting in high plasma concentrations which may contribute to the symptoms of the encephalopathy - use with caution. In severe liver disease reduce total daily dose to one third (give once daily). AST may be spuriously low while on metronidazole. Regular monitoring required if duration of treatment >10 days. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Manufacturer advises against a single high dose regimen during pregnancy. Available data does not indicate an increased risk of congenital malformations or adverse foetal effects associated with use in pregnancy. **Lactation** Hold breastfeeding during treatment with metronidazole.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Minocycline	<u>Treatment</u> 100mg BD <u>Prophylaxis</u> 100mg OD – BD	Can be useful for *S maltophilia, B. cepacia*, *A.xylosoxidans* Included in RBH NTM protocol. Advise patients to swallow caps/tabs whole, with plenty of water and in an upright position to avoid oesophageal irritation. Headaches and visual disturbances need investigating (benign intracranial hypertension reported with tetracyclines).	**Hepatic effects** If patients develop signs or symptoms of hepatotoxicity, minocycline should be discontinued. If treatment continues for >6 months, monitor every 3 months for hepatotoxicity. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Use in pregnancy is associated with perturbed fetal bone growth, congenital cataracts and discolouration of teeth in the child and may exacerbate fatty liver of pregnancy in the mother. Tetracyclines should be avoided after the first trimester unless compellingly indicated. **Lactation** There is not likely to be harm in short-term use of minocycline during lactation because milk levels are low and absorption by the infant is inhibited by the calcium in breastmilk. Short-term use of minocycline is acceptable in nursing mothers. As a theoretical precaution, avoid prolonged or repeat courses during nursing. Monitor the infant for rash and for possible effects on the gastrointestinal flora, such as diarrhoea or candidiasis. Black discolouration of breastmilk has been reported with minocycline

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Moxifloxacin	<u>Treatment</u> 400mg OD	Included in RBH NTM protocol. Not active against *P. aeruginosa* or MRSA Has been associated with QT interval prolongation therefore contra-indicated in: Congenital or documented acquired QT prolongation; Electrolyte disturbances, particularly in uncorrected hypokalaemia; Clinically relevant bradycardia; Clinically relevant heart failure with reduced left-ventricular ejection fraction; Previous history of symptomatic arrhythmias. The manufacturer advises that moxifloxacin should not be used concurrently with other drugs that prolong the QT interval: risks and benefits must be considered if this is deemed necessary. Other general advice on quinolones including effect on seizure threshold, photosensitivity and tendon damage also applies – see under 'ciprofloxacin.'	**Hepatic effects** Has been associated with life-threatening hepatotoxicity. Use is contraindicated in severe liver impairment and those with 5 x increase in transaminases. Patients should be advised to contact their doctor prior to continuing treatment if signs and symptoms of fulminant hepatic disease develop such as rapidly developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy. Liver function tests should be carried out in cases where possible liver dysfunction has occurred. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** No reports of moxifloxacin in pregnancy. Evidence of toxicity in animals would suggest that it should be avoided. **Lactation** Short-term use of moxifloxacin is acceptable in nursing mothers. However, it is preferable to use an alternate drug for which safety information is available.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Rifampicin	<u>Treatment</u> <50kg: 450mg BD >50kg: 600mg BD In *Mycobacterium avium* complex (MAC) infection, rifampicin is administered OD (600mg)	Second line for *S aureus*. Usually given with fusidic acid. May be useful as an adjunct in biofilm-associated infections. Included in RBH NTM protocol Advise patients to take at least 30 minutes before, or 2 h after food; stains body secretions red/brown. Rifampicin is a potent inducer of certain cytochrome P-450 enzymes. Co-administration with other drugs that are also metabolised through this system may accelerate the metabolism and reduce the activity of the other drugs. Caution should therefore be applied when prescribing rifampicin with other drugs, notably azoles, prednisolone, caspofungin, warfarin, antiepileptics, oral contraceptives, clarithromycin, immunosuppressants, simvastatin. This list is not exhaustive – if in doubt as to effects on other drugs, discuss with pharmacist.	**Hepatic effects** Take baseline LFT's and monitor for hepatotoxicity. Contra-indicated if the patient has jaundice. In liver dysfunction including CF liver disease, do not exceed 8mg/kg/day and ensure careful monitoring of liver function - especially serum alanine transaminase (ALT) and serum aspartate transaminase (AST) which should initially be carried out prior to therapy, weekly for two weeks, then every two weeks for the next six weeks. If signs of hepatocellular damage occur, rifampicin should be withdrawn. **Renal Impairment** **GFR 10-50mL/min** Dose as in normal renal function **GFR <10mL/min** 50% to 100% of normal dose	**Pregnancy** Few published studies do not indicate an increase in risk of congenital malformations. Neonatal haemorrhage has been reported following exposure to rifampicin in late pregnancy: maternal supplementation with vitamin K is recommended when rifampicin is administered during the last few weeks of pregnancy. Due to the reports of low birth weight in infants of women being treated with rifampicin, monitoring of fetal growth may be warranted. **Lactation** Excreted into breast milk in small amounts which are thought to represent a low risk to the nursing infant – no adverse effects in nursing infants have been reported.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Trimethoprim	Treatment 200 mg BD	May be useful for *B. cepacia* complex and MRSA in combination with other antibiotics. May cause depression of haematopoiesis, particularly when given over prolonged periods or in high doses. Monitor blood counts and advise the patient to report sore throats, fevers, and mouth ulcers, bruising or bleeding.	**Hepatic effects** Use with caution in patients with severe hepatic damage as changes may occur in the absorption and metabolism of trimethoprim. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** No overall increased risk of congenital malformation has been demonstrated with trimethoprim use in human pregnancy, although an increased risk of neural tube defects, cleft lip/palate and cardiac defects has been reported. Folate supplementation may reduce risks: high dose (5mg) folic acid is recommended in all women treated with trimethoprim during the first trimester as a precautionary measure. **Lactation** No reports found regarding neonatal toxicity following exposure to trimethoprim during lactation.

13.2: Intravenous antibiotics

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Amikacin	**OD dosing** (Non NTM) 15mg/kg once daily (Maximum 1500mg OD)	*Pseudomonas aeruginosa* (**OD dosing**)	**OD dosing** All doses, in 100mL sodium chloride 0.9% over 30 minutes	**OD dosing** Trough must be <5mg/L **Hepatic effects** No precautions necessary **Renal Impairment** **GFR 20-50mL/min** dose as in normal renal function **GFR < 20mL/min** 12mg/kg OD, adjusted according to trough level	**Pregnancy** No reports of congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. However, eighth cranial nerve toxicity in 2nd and 3rd trimester in human foetus after exposure to other aminoglycosides is well known and amikacin could potentially cause this. Close monitoring of levels is advised, if used. **Lactation** Compatible with breastfeeding.
	BD dosing 7.5mg/kg every 12 hours (Maximum 750mg BD)	NTM e.g. *Mycobacterium abscessus* (**BD dosing only**)	**BD dosing** <500mg, slow IV bolus ≥ 500mg, in 100mL sodium chloride 0.9% over 30 minutes	**BD dosing** Trough must be <5mg/L; Aim 1 hour post dose peak 20-30mg/L **Hepatic effects** No precautions necessary **Renal Impairment** **GFR 20-50mL/min** 6mg/kg BD, adjusted according to peak and trough levels **GFR<20mL/min** 6mg/kg every 12-24 hours (adjust frequency according to levels)	

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Aztreonam	2g every 8 hours (<35kg max. 50mg/kg TDS)	Narrow spectrum of activity against gram-negatives including *H.influenzae* and *P. aeruginosa*. No anti gram-positive activity, therefore usually used in combination with an aminoglycoside or colistin	Slow IV bolus over 3-5 minutes	**Hepatic effects** No specific precautions: Monitor closely **Renal impairment** **GFR 30-50mL/min** Dose as in normal renal function **GFR 10-30mL/min** 2g loading dose then reduce to 1g TDS **GFR <10mL/min** 2g loading dose then reduce to 500mg TDS	**Pregnancy** No reports of use in human pregnancy. Animal data suggest low risk. But absence of human pregnancy experience prevents a more complete assessment of the embryo-foetal risk. Use only if not possible to use antibiotics known to be safe in pregnancy. **Lactation** Compatible with breastfeeding
Cefoxitin	Usually 2-3g QDS (max 12g/day) (200mg/kg/day in 3-4 divided doses)	*Mycobacterium abscessus* **NOT active against *Pseudomonas aeruginosa*** Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	IV bolus over 3-5 minutes	**Hepatic effects** Transient elevations in AST, ALT, ALP and serum LDH have been reported; Jaundice has also been noted. **Renal impairment** **GFR 30-50mL/min** Max 2g TDS **GFR 10-30mL/min** 2g loading dose then 2g BD **GFR 5-10mL/min** 2g loading dose then 1g BD **GFR <5mL/min** 2g loading dose then 1g OD	**Pregnancy** No detectable teratogenic risk in a large 2001 study. Safe in all trimesters. **Lactation** Compatible with breastfeeding

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Ceftazidime	**Intermittent dosing** 2-3g every 8 hours. (<35kg Max. 50mg/kg TDS) **Continuous infusion** 12g over 24h	*Pseudomonas aeruginosa;* *B. cepacia;* *S. maltophilia*	**Intermittent dosing** IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes **Continuous infusion** Reconstitute each 2g vial with 20mL WFI. Infuse 4g (40mL) over 8h then repeat.	**Hepatic effects** No need to adjust doses in mild to moderate hepatic impairment. Transient elevations in one or more liver enzymes common; jaundice has been reported. Monitor closely in severe impairment. **Renal impairment** **GFR 31-50mL/min** 2g BD **GFR 16-30mL/min** 2g OD **GFR 6-15mL/min** 1g OD **GFR <5mL/min** 1g every 48h	**Pregnancy** No detectable teratogenic risk in a large 2001 study. Safe in all trimesters. **Lactation** Compatible with breastfeeding.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Chloramphenicol	12.5-25mg/kg QDS (usually 500mg). Max. 1g QDS Avoid repeat courses within 3 months of last course.	Anecdotal reports of a clinical response in patients with *P.aeruginosa* and *B.cepacia* complex	Bolus over at least 1 minute. Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	**Hepatic effects** Avoid if possible in hepatic impairment. If not possible, reduced dose may be required to maintain trough level <10mg/L. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function Manufacturers recommend monitoring levels in patients with renal impairment. Therapeutic range: peak = 10-20 mg/L (0.5-1.5h after IV dose); trough = 5-10 mg/L.	**Pregnancy** Not associated with increased incidence of congenital malformations. Concerns that use near term may be associated with a risk of neonatal Gray Baby Syndrome are not supported by evidence. However, UK recommendations are that during pregnancy, the use of systemic chloramphenicol should be reserved for life-threatening illness. **Lactation** An alternate drug is preferred to chloramphenicol during breastfeeding, especially while nursing a newborn or preterm infant. If the mother must receive chloramphenicol during nursing, monitor the infant for gastrointestinal disturbances and adequacy of nursing. Monitoring of the infant's complete blood count and differential is advisable. In some cases, discontinuation of breastfeeding might be preferred.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Ciprofloxacin	400mg every 12 hours	*P. aeruginosa*	Infuse over 60 minutes	**Hepatic effects** No dose adjustments necessary in hepatic impairment. Increased transaminases and bilirubin are uncommon. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** 400mg BD **GFR <10mL/min** 200mg BD	**Pregnancy** Limited evidence does not suggest any increased risk of adverse pregnancy outcomes – treatment should not be withheld if indicated. **Lactation** Fluoroquinolones have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, recent studies indicate little risk. The calcium in milk might prevent absorption of the small amounts of fluoroquinolones in milk, but insufficient data exist to prove or disprove this.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Colistimethate	<40kg – 1MU every 8 hours > 40kg – 2MU every 8 hours	*P. aeruginosa* **NOT active against *B. Cepacia complex***	Bolus administration is routine practice at RBH on respiratory wards. **Via totally implanted venous access device (TIVAD, *Port*):** Reconstitute with 10-20mL water for injections and administer over 5 minutes. **Via venflon/long line:** Reconstitute with 20-40mL water for injections and administer over 5 minutes. Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	**Hepatic effects** No specific precautions **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** 1MU BD (max. 50% of usual dose for weight) **GFR <10mL/min** 1MU every 18-24 hours (max. 30% usual dose for weight)	**Pregnancy** There are no adequate data from the use of colistimethate sodium in pregnant women. Single dose studies in human pregnancy show that colistimethate sodium crosses the placental barrier and there may be a risk of foetal toxicity if repeated doses are given to pregnant patients. Animal studies are insufficient with respect to the effect of colistimethate sodium on reproduction and development. Colistimethate sodium should be used in pregnancy only if the benefit to the mother outweighs the potential risk to the foetus[SPC]. **Lactation** Colistimethate is excreted into breastmilk at a low level which may cause modification of infant bowel flora[BRIGGS].

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Co-trimoxazole	960mg – 1.44g every 12 hours (<35kg Max. 27mg/kg)	Used mainly for *S maltophilia*. Useful active against *S. aureus*, *H. influenzae* and may be useful for *B. cepacia*.	960mg – 250ml 0.9% sodium chloride over 60 minutes 1.44g – 500ml 0.9% sodium chloride over 90 minutes	**Hepatic effects** Increased LFTs and bilirubin, hepatic necrosis and cholestatic jaundice have been rarely reported. No data are available relating to dosage in patients with impaired hepatic function. Contra-indicated in patients showing marked liver parenchymal damage. **Renal Impairment** **GFR 30-50mL/min** Dose as in normal renal function **GFR <30mL/min** 50% of normal dose, i.e. 480 – 720mg BD	**Pregnancy** Potential increased risk of hyperbilirubinaemia with sulphonamide-containing medicines during pregnancy in neonates with other risk factors. No overall increased risk of congenital malformation has been demonstrated with trimethoprim use in human pregnancy, although an increased risk of neural tube defects, cleft lip/palate and cardiac defects has been reported. Folate supplementation may reduce risks: high dose (5mg) folic acid is recommended in all women treated with trimethoprim (and therefore co-trimoxazole) during the first trimester as a precautionary measure. **Lactation** No reports found regarding neonatal toxicity following exposure to trimethoprim during lactation. With healthy, full-term infants it appears acceptable to use sulfamethoxazole and trimethoprim during breastfeeding after the newborn period.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Flucloxacillin	1-2g every 6 hours (50mg/kg QDS)	*S. aureus*	IV bolus over 3-5 minutes	**Hepatic effects** Changes in LFT results may occur: reversible when treatment is discontinued. Hepatitis and cholestatic jaundice have been reported, and are not related to dose or route of administration; administration for more than two weeks and increasing age are risk factors. The onset of these effects may be delayed for up to two months post-treatment; in several cases the course of the reactions has been protracted and lasted for some months. Contraindicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction. Use with caution in patients with hepatic dysfunction. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function up to a total daily dose of 4g Monitor urine for protein at high doses	**Pregnancy** Considerable clinical experience has not indicated adverse fetal effects when flucloxacillin is used in pregnancy. **Lactation** Penicillins and cephalosporins are the antibiotics of choice during breastfeeding. However, trace quantities of flucloxacillin can be detected in breast milk: the possibility of hypersensitivity reactions must be considered in breast-feeding infants.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Fosfomycin	4g every 6 hours	*Pseudomonas aeruginosa*	250ml 5% dextrose over 60 minutes Can also be infused in 200mL WFI: Reconstitute the 4g vial, withdraw two 2g aliquots and add to each of two 100mL WFI – infuse sequentially over 30 minutes (total 60 minutes)	**Hepatic effects** Temporary increases in transaminases and alkaline phosphatase have been observed. **Renal Impairment** **GFR 20-40mL/min** 4g every 12 hours **GFR 10-20mL/min** 4g every 24 hours **GFR <10mL/min** 4g every 48 hours	**Pregnancy** Lack of teratogenicity in animals and apparently safe use during human pregnancy appear to indicate that it presents a low risk to foetus – compatible with pregnancy. **Lactation** A small quantity passes into breast milk – although limited human data, probably compatible.
Meropenem	2g every 8 hours (Reduce to 1g TDS if adverse effects)	*Pseudomonas aeruginosa*; *B.cepacia* complex; *Mycobacterium abscessus*	Each 1g vial must be reconstituted with 20ml water and given as an IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	**Hepatic effects** Increased transaminases, ALP and lactate dehydrogenase are common; increased bilirubin uncommon: monitor in those with pre-existing liver disorders. No dose adjustment is necessary in hepatic impairment; however, local practice is to try 1g TDS in those with persistently elevated transaminases on higher dose. **Renal Impairment** **GFR 20-50mL/min** 2g BD **GFR 10-20mL/min** 1g BD **GFR <10mL/min** 1g OD	**Pregnancy** There is limited human data, animal studies suggest low risk. Animal studies have shown no evidence of impaired fertility or foetal harm. The near absence of published human pregnancy data doesn't allow an assessment of embryo-foetal risk. Imipenem-cilastin is considered safe to use after 28 weeks gestation and meropenem is most likely can be classed similarly. The foetal risk pre-28 weeks is unknown. **Lactation** No reports of use of meroepem during lactation. Potential effect on infant unknown but probably compatible.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Piperacillin/ tazobactam	4.5g every 6 – 8 hours (Max 4.5g QDS) (90mg/kg)	*Pseudomonas aeruginosa*	IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	**Hepatic effects** Monitor hepatic function. No dosage adjustment necessary in hepatic impairment. Increases in transaminases are uncommon; increased bilirubin, ALP, GGT and hepatitis are rare. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Max 4.5g TDS **GFR <10mL/min** 4.5g BD	**Pregnancy** Human data are very limited. No foetal harm was observed in animals. There is substantial experience with penicillins in human pregnancy that have shown this class of drugs are safe. Tazobactam is probably safe in pregnancy. **Lactation** Although no information is available on the use of piperacillin and tazobactam during breastfeeding, limited information indicates that maternal doses of piperacillin produce low levels in milk that are not expected to cause adverse effects in breastfed infants. Piperacillin and tazobactam is acceptable to use during breastfeeding.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Teicoplanin	400mg every 12 hours for 3 doses then 400mg once daily	Methicillin resistant *S. aureus* (MRSA)	Reconstitute with diluent supplied. Usually given by IV bolus over 3-5 minutes. Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	**Hepatic effects**[i] May cause transient abnormalities in transaminases and ALP. Liver function should be monitored, but no dosage adjustments necessary in impairment. **Renal Impairment**[ii] **GFR 20-50mL/min** Give normal loading dose then dose as in normal renal function **GFR 10-20mL/min** Give normal loading dose then dose as in normal renal function **GFR <10mL/min** Give normal loading dose then 400mg every 48h	**Pregnancy** No adequate data from the use of teicoplanin in human pregnancy. Studies in animals have shown reproductive toxicity at high doses. The potential risk for humans is unknown. Teicoplanin should not be used during pregnancy unless clearly necessary[spc]. **Lactation** It is not known whether teicoplanin is excreted in human breast milk. The excretion of teicoplanin in milk has not been studied in animals[spc].

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Temocillin	2g every 12 hours	*B. cepacia* complex **NO activity against *Pseudomonas aeruginosa***	IV bolus over 3-5 minutes Can be given as an infusion: add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes.	**Hepatic effects** Limited experience in patients with impaired hepatic function has not indicated a need for a reduction in dosage. **Renal Impairment** **GFR 30-50mL/min** Dose as in normal renal function **GFR 10-30mL/min** 2g OD **GFR <10mL/min** 2g every 48h	**Pregnancy** Animal studies with temocillin have shown no teratogenic effects. There is no experience of temocillin in human pregnancy. However, temocillin is a penicillin;this class of drugs are known to be safe in all trimesters. **Lactation** There is no information on the use of temocillin in lactation. However it is known that penicillins are compatiblie with breastfeeding.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Tigecycline	50mg every 12 hours (we do not routinely give loading dose due to nausea) Reduce to 25mg every 12 hours if 50mg not tolerated	*Mycobacterium abscessus* Resistant *achromobacter xyloxidans* *Stenotrophomas maltophilia*	Add reconstituted drug to 100mL sodium chloride 0.9% and administer over 30 minutes. Ensure regular IV ondansetron (or alternative if required) also prescribed – highly emetogenic – risk of treatment failure if cannot tolerate.	**Hepatic effects** Elevated transaminases and bilirubin common. Jaundice and liver injury (mostly cholestatic) uncommon. No dose reduction required in mild to moderate liver impairment (Child-Pugh Class A and B). In severe liver disease (Child-Pugh Class C), 100mg loading dose then 25mg BD. Use with caution and monitor clinical response. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function	**Pregnancy** No reports of the use of tigecycline in human pregnancy. In one animal species exposures close to those in humans that did not cause maternal toxicity did result in reduced foetal weight and minor skeletal abnormalities. Tigecycline crosses the placenta of rats and rabbits and enters foetal tissue including bony structures. Tigecycline can permanently discolour teeth if used in the second half of pregnancy. Use in 1st trimester does not represent a major risk to foetus but use in 2nd and 3rd trimesters should be avoided. **Lactation** There are no reports of the use of tigecycline use during human lactation. It is likely to be excreted into breast milk but there may be little or no systemic exposure.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Timentin (ticarcillin/ clavulanic acid)	3.2g every 6 hours (80mg/kg)	*Pseudomonas aeruginosa* May be useful for *Stenotrophomonas maltophilia*	Add reconstituted drug to 100mL water for injections and administer over 30 minutes. (If hyponatraemia is a problem, can be added to 100mL 5% dextrose to administer)	**Hepatic effects** Monitor liver function: can cause cholestatic jaundice, increase in LFTs and transient hepatitis. Cholestatic jaundice may occur during use or soon after treatment cessation. Use with caution in patients with evidence of severe hepatic dysfunction. **Renal Impairment** **GFR 30-50mL/min** 3.2g TDS **GFR 10-30mL/min** 1.6g TDS **GFR <10mL/min** 1.6g BD	**Pregnancy** No reports linking the use of ticarcillin have been reported. Although experience is limited, all penicillins are considered low risk in pregnancy. Several studies have described the safe use of clavulanic acid in pregnant women. **Lactation** Compatible with breastfeeding.
Tobramycin	7mg/kg once daily Max dose 660mg once daily.	*Pseudomonas aeruginosa* *Burkhoderia cepacia* complex	100ml 0.9% sodium chloride over 30 minutes	GFR 20-50 – 3mg/kg od Avoid if GFR < 20ml/min	**Pregnancy** No reports linking the use of tobramcyin with congenital defects. Not teratogenic in 2 animal species. Ototoxicity has not been reported as an effect of in utero exposure. However, eighth cranial nerve toxicity in the foetus is well know following exposure to other aminoglyosides and may potentially occur with tobramcyin. **Lactation** Compatible with breastfeeding.

Drug	Dose	Relevant Antimicrobial Activity of Interest	Administration	Liver/Renal considerations and monitoring	Pregnancy & Lactation
Vancomycin	1g every 12 hours	MRSA	250ml 0.9% sodium chloride over 100 minutes	**Hepatic effects** No dose adjustments necessary. **Renal Impairment** (starting dose; adjust according to levels) **GFR 20-50mL/min** 500mg-1g od-bd **GFR 10-20mL/min** 500mg-1g every 24 to 48 hours **GFR <10mL/min** 500mg-1g every 48 to 96 hours **Therapeutic Drug Monitoring** Trough levels should be 10-15mg/L. Check trough level just before 4th dose. Level <10mg/L: increase maintenance dose by 500mg daily and repeat level after 48h. Level 15-20mg/L: continue if patient tolerating. Level 20-25mg/L: if next dose not yet given, reduce by 500mg daily without omitting any doses; if the dose has already been given, omit one dose and then reduce maintenance dose by 500mg daily.	**Pregnancy** There are no known cases of congenital defects. The manufacturer has received reports of use in pregnancy without any adverse foetal effects. **Lactation** Limited information indicates that vancomycin produces low levels in milk and it would not be expected to be absorbed or cause any adverse effects in breastfed infants.

13.33: Oral Antifungals

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Fluconazole	Candidiasis associated with antibiotic use: 100mg daily for duration of antibiotic course	Patients should be warned about the potential for dizziness and should be advised not to drive or operate machines if any of these symptoms occur.	**Hepatic effects** Monitor liver function. Hepatotoxicity including raised LFTs is usually reversible on discontinuation. Hepatic necrosis rarely observed. Toxicity increased with concomitant use of hepatotoxic drugs. Discontinue if clinical signs/symptoms occur. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** 50% of normal dose	**Pregnancy** Use of fluconazole during 1st trimester appears to be teratogenic with continuous daily doses of 400mg/day or more; malformations may resemble those observed in Antley-Bixler Syndrome. Due to limited available safety data, high dose fluconazole use during pregnancy should be avoided unless compellingly indicated. **Lactation** Compatible with breastfeeding – if possible, the dose should be taken at night after the last breast-feed.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Itraconazole	Usual starting dose: 200 mg BD May be increased according to levels	Capsules are poorly absorbed in CF. Use liquid where possible (limited due to taste). Liquid should ideally be taken one hour before food.[iii] Capsules should be taken immediately after a meal for maximal absorption or with acidic drink e.g. cola/orange in patients taking acid secretion suppressors.	**Hepatic effects** Prolonged half-life in cirrhotic patients whilst oral bioavailability is decreased – adjust dose according to levels. Elevations in liver enzymes, hepatitis, serious hepatotoxicity, fatal acute liver failure is very rare. Monitor LFTs during treatment and should be stopped if signs or symptoms suggestive of hepatitis are present. If pre-existing liver disease or has experienced liver toxicity with other drugs then treatment must only be started if benefit exceeds risk of liver injury. **Renal impairment** **(all levels)** Dose as in normal renal function **Therapeutic Drug Monitoring** Target trough 0.5 – 2.0mg/L (parent molecule) or 1.0 – 4.0mg/L (parent molecule + metabolite. (Parent + metabolite indicates potential total biological activity).	**Pregnancy** Human pregnancy data suggests that the risk of foetal toxicity is low. The animal data cannot be adequately interpreted because maternal toxicity was evident and comparisons with human data were based on body weight. Safest to avoid, especially in 1st trimester. **Lactation** Excreted into breast milk - effects of long term exposure on the infant has not been studied, therefore not recommended.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Voriconazole	<40 kg: 200 mg BD for 1 day then 100 mg BD >40 kg: 400 mg BD for 1 day then 200 mg BD Doses may be increase according to levels. Non linear pharmacokinetics: increase doses cautiously – refer to pharmacist for advice on doses >200mg BD. (We have occasionally increased cautiously to 400mg BD)	Photosensitivity – avoid exposure to sunlight. Use high factor sun block up to 4 weeks post treatment. Refer to dermatologist if photosensitivity reaction occurs. Risk of squamous cell carcinoma of the skin has been reported on long term use in patients with photosensitivity and other risk factors. Monitor visual function and renal function with long term use.	**Hepatic effects** Associated with elevations in LFT's and clinical signs of liver damage such as jaundice. No dose adjustment is necessary in patients with acute hepatic injury manifested by elevated LFT's (monitor for further increases). Patients with hepatic impairment must be carefully monitored for drug toxicity. Mild to moderate hepatic impairment (**Child-Pugh A and B**): Standard loading dose; 50% usual maintenance dose. Severe hepatic impairment (**Child-Pugh C**): No information available. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function **Therapeutic Drug Monitoring** Serum levels should be measured after 3 days of commencing therapy or dose changes, take sample just before the next oral dose. Dose escalation is advised for any level less than 1.3mg/L.	**Pregnancy** No reports in human pregnancy available; animal data suggests risk of toxicity and teratogenicity. Avoid. **Lactation** Voriconazole is expected to be excreted into breast-milk therefore potential for toxicity in nursing infants, especially during the neonatal period. Women taking voriconazole should avoid breastfeeding.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Posaconazole	400 mg BD May need to adjust according to levels – we have occasionally increased to 400mg TDS.	Take dose immediately following a meal to enhance absorption. If not possible, may need to use 200mg QDS dosing.	**Hepatic effects** Monitor liver function before and during treatment. Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) demonstrate an increase in plasma exposure, but do not suggest that dose adjustment is necessary – monitor levels.[iv] Increases in liver enzymes & bilirubin may be observed and are reversible on discontinuation. Hepatitis, jaundice, hepatomegaly, hepatic failure, cholestasis also observed. **Renal Impairment** **(all levels)** Dose as in normal renal function[v] **Therapeutic Drug Monitoring** Serum levels should be monitored where indicated e.g. interacting drug commenced or efficacy not observed – random sample after 1-2 weeks on oral therapy should be >0.7mg/L.	**Pregnancy** There are no reports on use in pregnancy. Animal data suggest risk of toxicity. Avoid during pregnancy, especially in 1st trimester. **Lactation** No reports in human lactation. Avoid as potentially toxic to infant.

13.4: Intravenous Antifungals

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Amphotericin B Liposomal (Ambisome®)	*Aspergillus* spp. *Candida* spp.	**Test dose:** 1mg (Day 1 only)	Infuse from prepared amphotericin (see below) over 10 minutes; stop the infusion and observe patient for 30 minutes. If no reaction proceed with remainder of the infusion.	**Hepatic effects** No data to indicate need to alter dose in hepatic dysfunction. Monitor hepatic function: abnormal LFT's, hyperbilirubinaemia and increased ALP common. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function Use with caution with other nephrotoxic antibiotics e.g. aminoglycosides, colomycin.	**Pregnancy** No adverse effects have been reported in exposed human embryos and foetuses. **Lactation** No reports regarding use during human lactation have been located.[vi] However, as oral absorption is minimal, and due to high protein binding and molecular weight as well as its use in paediatrics, it is unlikely the amount in milk would be clinically relevant to a breastfeeding infant.
		If tolerated: Day 1: 1mg/kg OD Thereafter 3mg/kg OD – can be increased to 5mg/kg OD if necessary.	Dilute to final concentration 0.2 – 2mg/L with 5% glucose and infuse over 30-60 minutes. CIVAS available during pharmacy opening hours.		

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Caspofungin	*Aspergillus* spp. *Candida* spp. *Exophiala* spp.	Single 70mg loading dose, then: <80kg: 50mg OD >80kg: 70mg OD	Add reconstituted drug to 250mL sodium chloride 0.9% and administer over 60 minutes.	**Hepatic effects** Monitor liver function: elevations in ALT, AST, ALP and bilirubin are common. Cholestasis, hepatotoxicity and abnormal hepatic function uncommon. Mild hepatic impairment (**Child-Pugh A**): No dose adjustment necessary. Moderate hepatic impairment (**Child-Pugh B**): 70mg loading dose then 35mg on Severe impairment (**Child-Pugh C**): No clinical experience. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function	**Pregnancy** No reports in human pregnancy available; animal data suggest risk, especially if exposure occurs in the 1st trimester. If indicated, maternal treatment should avoid the 1st trimester if possible. **Lactation** No data available for human milk. Oral bioavailablilty reported to be poor therefore unlikely an infant would absorb enough to be clinically relevant. [vii] As the risk of harm from exposure to caspofungin appears to be low, women being treated with caspofungin should be allowed to breast feed. Infants should be monitored for signs and symptoms of histamine release and GI complaints.

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Fluconazole	*Candida spp.*	400mg OD (<35kg maximum 12mg/kg/d)	Administer at a rate not exceeding 5-10mL/minute (10-20mg/minute).	**Hepatic effects** Monitor liver function. Hepatotoxicity including raised LFTs is usually reversible on discontinuation. Hepatic necrosis rarely observed. Toxicity increased with concomitant use of hepatotoxic drugs. Discontinue if clinical signs/symptoms occur. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** 50% of normal dose	**Pregnancy** Use of fluconazole during 1st trimester appears to be teratogenic with continuous daily doses of 400mg/day or more; malformations may resemble those observed in Antley-Bixler Syndrome. Due to limited available safety data, high dose fluconazole use during pregnancy should be avoided unless compellingly indicated. **Lactation** Compatible with breastfeeding – if possible, the dose should be taken at night after the last breast-feed.

Drug	Relevant Activity of Interest	Dose	Administration	Liver/Renal considerations and TDM	Pregnancy & Lactation
Voriconazole	*Aspergillus* spp. *Candida* spp *Exophiala* spp. *Scedosporium* spp.	Loading dose: 6mg/kg 12 hourly for 2 doses then; Maintenance dose: 4mg/kg BD	Further dilute reconstituted voriconazole to 0.5 – 5mg/mL in 0.9% sodium chloride. Administer at a rate of not more than 3mg/kg/hour over 1-3h.	**Hepatic effects** Associated with elevations in LFT's and clinical signs of liver damage such as jaundice. No dose adjustment is necessary in patients with acute hepatic injury manifested by elevated LFT's. Patients with hepatic impairment must be carefully monitored for drug toxicity. Mild to moderate hepatic impairment (**Child-Pugh A and B**): Standard loading dose; 50% usual maintenance dose. Severe hepatic impairment (**Child-Pugh C**): No information available. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Dose as in normal renal function	**Pregnancy** No reports in human pregnancy available; animal data suggests risk of toxicity and teratogenicity. Avoid. **Lactation** Voriconazole is expected to be excreted into breast-milk therefore potential for toxicity in nursing infants, especially during the neonatal period. Women taking voriconazole should avoid breastfeeding.

13.5: Inhaled Antimicrobials

13.5.1: Nebulised Antimicrobials

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Amikacin	*Mycobacterium abscessus*	500 mg BD Use 500mg/2mL IV preparation (we use Hospira UK brand)	Vibrating mesh nebuliser	Use neat	Possible adverse effects: aminoglycoside-related ototoxicity, bronchoconstriction, mouth soreness. Once opened, ampoules and vials should be used immediately Stop if tinnitus or hearing loss develops. Stop temporarily if on IV aminoglycosides.	There have been no reports linking the use of amikacin to congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. Eighth cranial nerve toxicity in the fetus has, however, been reported after exposure to other aminoglycosides (kanamycin and streptomycin). Amikacin could potentially cause this, however, as absorption following inhalation of aminoglycosides is likely to be minimal and the maternal systemic concentration low, amikacin may be considered if maternal benefits outweigh risk to foetus.
			Jet nebuliser and compressor	Further dilute to 4mL with sodium chloride 0.9%		

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Amphotericin (Fungizone® 50mg IV preparation)	*Aspergillus fumigatus*	Initially 5mg twice daily. Increase in steps of 5mg up to 0.5mg/kg (max 25mg) twice daily. There is usually no need to use the liposomal formulation (Ambisome®)for nebulisation, however, this may be considered if essential in those who do not intolerant Fungizone®	Jet nebuliser	Reconstitute a 50mg vial with 10mL water for injections to produce a 5mg/mL solution. Withdraw the required amount and further dilute if necessary to minimum 3mL with water for injections. DO NOT mix with sodium chloride 0.9%	Once reconstituted, the remainder of the vial may be stored in a refrigerator for up to 24h at 2-8°C for the next 1-2 doses.	No reports linking the use of amphotericin with congenital defects located. Compatible with pregnancy.

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Aztreonam Lysine (Cayston®)	*Pseudomonas aeruginosa*	75 mg TDS on alternate months	Altera Nebuliser Handset and Altera Aerosol Head (supplied with the drug) connected to an Altera Control Unit or an eFlow rapid Control Unit	Reconstitute the lyophilised aztreonam lysine with 1mL solvent supplied (0.17% w/v sodium chloride)	Once reconstituted, use immediately. Powder vial and solvent ampoule must be stored in a refrigerator (2-8°C). May be stored outside a refrigerator at up to 25°C for up to 28 days.	There are no data from the use of aztreonam in pregnant women, however, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Systemic concentration of aztreonam following inhaled administration of nebulised aztreonam is low. Furthermore, beta lactam antibiotics can be used during pregnancy when strongly indicated. Nebulised aztreonam may therefore be used during pregnancy where the clinical condition of the woman requires treatment.
Ceftazidime	*Burkholderia cepacia*	1g bd	Jet nebuliser only Mesh nebuliser systems (i-Neb ADD and eFlow) should not be used	Reconstitute a 1g vial with 3mL water for injections		If clinically indicated, cephalosporins may be used at any stage during pregnancy.

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Colistimethate sodium (colistin) (Colomycin®, Promixin®)	Eradication/suppression of *Pseudomonas aeruginosa* lung infection	iNeb: 1 million units BD (Promixin)	With i-Neb ADD System only (Grey chamber)	Reconstitute 1MU Promixin vial with 1mL sodium chloride 0.9%	Colomycin® can be reconstituted with salbutamol (2.5 to 5mg) if the patient experiences bronchoconstriction	There is no data on nebulised colistin but experience suggests this is safe in pregnancy.
		Other nebulisers: 2 million units BD (we have used TDS in certain circumstances)	eFlow Jet nebuliser	Reconstitute the contents of the 2 million unit vial with 2-4mL (depending on nebuliser device) sodium chloride 0.9% or water for injections		
Meropenem (500mg powder for reconstitution IV preparation)	*Mycobacterium abscessus; Burkholderia cepacia*	250mg BD	E-Flow Jet nebuliser and compressor The i-Neb ADD system should not be used	Reconstitute a 500mg vial with 10mL sodium chloride 0.9% and withdraw 5mL (250mg).	If reconstituted to give a final concentration of 50mg/mL with sodium chloride 0.9%, the remainder of the vial can be stored in a fridge at 2-8°C for up to 18 hours for the next dose.	No information available in human pregnancy therefore use cannot routinely be recommended. Animal studies have shown no evidence of impaired fertility or foetal harm. Meropenem by nebulisation should be considered if the maternal benefit outweighs the risk to the foetus.
				Alternatively, can be reconstituted with Water for Injections (2nd line) and withdraw 5mL (250mg) (note reduced expiry time).	If reconstituted to give a final concentration of 50mg/mL with water for injections, the remainder of the vial can be stored in a fridge at 2-8°C for up to 12 hours for the next dose.	

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Taurolidine	*Burkholderia cepacia* (unresponsive to standard antibiotic options)	Usually 2-5ml of the 2% solution BD	Jet nebuliser and compressor	Use neat	Once in use, each bottle may be stored in a refrigerator and used for up to 7 days.	No information available in human pregnancy therefore use cannot routinely be recommended.
Temocillin	*Burkholderia cepacia*	1g BD	Jet nebuliser and compressor	Reconstitute a 1g vial with 3mL water for injections		No information available in human pregnancy therefore use cannot routinely be recommended. However, penicillins are known to be safe in pregnancy and lactation.

Drug	Indication	Dose	Nebuliser devices	Reconstitution/ dilution	Counselling and storage	Pregnancy and lactation
Tobramycin preservative-free solution for nebulisation BRAMITOB® or TOBI®	Long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa*	300mg BD on alternate months	i-Neb (Lilac chamber) eFlow Jet nebuliser and compressor	Ready to use solution. Do not mix with any other solution for nebulisation.	BD dosing should ideally be 12 hourly. If a shorter interval between morning & evening doses is needed, the interval should not be less than 6 hours. Store at 2 – 8 ºC, in the original container. After removal from refrigerator, TOBI® pouches (intact or opened) may be stored at up to 25ºC for **up to 28 days;** Bramitob® pouches (intact or opened) may be stored at up to 25ºC for **up to 3 months** Stop if tinnitus or hearing loss develops. Stop temporarily if on IV aminoglycosides.	There have been no reports linking the use of tobramycin to congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. Eighth cranial nerve toxicity in the fetus has, however, been reported after exposure to other aminoglycosides. Tobramycin could potentially cause this, however, as absorption following inhalation of aminoglycosides is likely to be minimal and the maternal systemic concentration low, tobramycin may be considered if maternal benefits outweigh risk to foetus.

Section 5.2 Dry Powder Inhalers

Drug	Indication	Dose	Counselling and storage	Pregnancy and lactation
Colobreathe®	Long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa*	1,662,500 units BD	N/A	There is no data on nebulised colistin but experience suggests this is safe in pregnancy.
Tobi Podhaler®	Long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa*	112mg BD	N/A	There have been no reports linking the use of tobramycin to congenital defects. Ototoxicity has not been reported as an effect of in utero exposure. Eighth cranial nerve toxicity in the fetus has, however, been reported after exposure to other aminoglycosides. Tobramycin could potentially cause this, however, as Systemic exposure following inhalation of TOBI Podhaler is very low, it may be considered if maternal benefits outweigh risk to foetus. The manufacturer recommends that patients who use TOBI Podhaler during pregnancy, or become pregnant while taking TOBI Podhaler, should be informed of the potential hazard to the foetus.

Section 6: Mucolytics

Drug	Route	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy
Hypertonic saline solution Nebusal® 7% 4mL amps	Nebulised pre-physio	Adults: 4mL of 3.5% or 7% BD	Pre-treat with bronchodilator For 3.5% solution: dilute 7% solution with an equal volume of water for injections	**Hepatic effects** Minimal systemic absorption so very unlikely to affect liver function **Renal Impairment** Minimal systemic absorption so very unlikely to affect renal function	**Pregnancy** Safe in all trimesters. **Lactation** Safe in breastfeeding
N-acetylcysteine 20% (200 mg/mL) injection	Nebulised 30 min pre-physio	3 – 4mL of 50 – 100 mg/mL 2 – 4 times a day	NOT granules. Forewarn patients – tastes and smells unpleasant. 50 mg/mL: dilute 1mL 20% with 3mL WFI 100 mg/mL: dilute 1.5mL 20% with 1.5mL WFI If only a proportion of the ampoule is used the remainder may be transferred to a plastic syringe, *stored in a refrigerator at 2-8°C up to 96 hours* for subsequent doses.	**Hepatic effects** Minimal systemic absorption so very unlikely to affect liver function **Renal Impairment** Minimal systemic absorption so very unlikely to affect renal function	**Pregnancy** No experience as mucolytic in human pregnancy but likely compatible **Lactation** Compatible with breastfeeding
Dornase alfa (rhDNase) Pulmozyme®	Nebulised 1 hour pre-physio	2.5mg OD. May be increased to BD if required	3 month trial to assess effect	**Hepatic effects** Minimal systemic absorption so very unlikely to affect liver function **Renal Impairment** Minimal systemic absorption so very unlikely to affect renal function	**Pregnancy** No human data. Animal data suggests no placental transfer. Our experience of use in pregnancy suggests safe in pregnancy. **Lactation** Compatible with breastfeeding

Drug	Route	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy
Mannitol Bronchitol®	Inhaled 30 min pre-physiotherapy.	400mg (10 x 40mg capsules) BD	Use after dornase alfa, if applicable.	**Hepatic effects** Mannitol has not specifically been studied in patients with impaired hepatic function. Data from studies suggest that no dose adjustments are required. **Renal Impairment** Mannitol has not specifically been studied in patients with impaired renal function. Data from studies suggest that no dose adjustments are required.	**Pregnancy** There are limited data from the use of mannitol in pregnant women. Animal studies do not indicate direct or indirect harmful effects..As the effects of a possible hyperresponsive reaction on the mother and/or foetus are unknown, caution should be exercised when prescribing mannitol to pregnant women. **Lactation** Unknown if excreted into breastmilk.

Section 7: Gastrointestinal

Section 7.1: Pancreatic Enzyme Replacement Therapy (PERT)

Drug	Dose		Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Creon Micro (Protease 200 units, lipase 5000 units, amylase 3600 units per 100mg)	Pancreatic insufficiency	Initially 100mg (1 measure) with each meal	Dose should be gradually increased according to response and tolerance Capsules should be swallowed whole or may be opened and both granules and capsules must be taken with acidic fluid e.g. orange, apple or pineapple juice or soft food e.g apple puree or yogurt, but without chewing and taken immediately.	**Hepatic Effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** No clinical data on exposed pregnancies available, although animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. **Lactation** Can be used during breast – feeding.
Creon 10,000, 25, 000 and 40,000		1-2 capsules initially with each meal			
Pancrex V powder (protease 1400 units, lipase 25,000 units, amylase 30,000 units/g)	Pancreatic insufficiency	0.5-2g before each meal & snack	Dose should be gradually increased according to response and tolerance Can be swallowed dry and washed down with a drink or mixed with water or milk Can be given via Nasogastric tube by mixing the powder in 10-20ml of water.	**Hepatic Effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Although manufacturer does not recommend unless clearly necessary, animal studies show no evidence for any absorption of porcine pancreatic enzymes. Therefore, no reproductive or developmental toxicity is to be expected. **Lactation** Where necessary can be used in breast-feeding.

Section 7.2: Lipid-soluble vitamins

Drug	Dose	Liver/Renal considerations	Pregnancy & Lactation
Vitamin BPC	2-4 capsules OD	**Hepatic effects** Enhanced susceptibility to effects of vitamin A in hepatic impairment. **Renal Impairment** Use with caution in renal impairment.	**Pregnancy** Can be used during pregnancy. **Lactation** Can be used during breast-feeding.
Vitamin A&D	2-3 capsules OD	**Hepatic effects** Enhanced susceptibility to effects of Vit A in hepatic impairment **Renal Impairment** Use with caution in renal impairment.	**Pregnancy** Vitamin A&D capsules at RBH contain 450units of Vitamin D & 4500 units of Vitamin A. Maximum dose compatible with pregnancy and specifically CF patients is less than 10,000units/day of Vitamin A. Therefore maximum dose 2 Vitamin A&D capsules OD during pregnancy. **Lactation** Maximum dose of 2 capsules OD during breastfeeding.
High dose Vitamin D (colecalciferol)	Refer to Trust Guidelines for Vitamin D in Adult CF pts	**Hepatic effects** No dose adjustment in hepatic impairment **Renal Impairment** Use with caution in renal impairment.	**Pregnancy** Can use in pregnancy until maternal levels are normal. Plasma calcium and vitamin D levels must be regularly monitored to prevent hypercalcaemia. Limited data on high dose in pregnancy, however, evidence of deficiency during pregnancy has been associated with maternal and fetal complications such as pre-eclampsia, gestational diabetes, increase incidence of pre-term delivery, stillbirth and poor foetal bone development and growth retardation. High doses with normal levels of vitamin D, and hypercalcaemia can lead to complications. **Lactation** Limited concentrations enter into breast milk. Mothers deficient in Vitamin D may not provide sufficient levels to the infant & impede bone mineralisation. Excessive doses may lead to hypercalcaemia in the infant, therefore best to avoid in breast-feeding.

Drug	Dose	Liver/Renal considerations	Pregnancy & Lactation
Vitamin E (Tocopheryl acetate) Vita E gel capsules	200iu (134mg) – 400iu (268mg) OD	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Safe in preganancy. **Lactation** Can be used in breast-feeding at doses of no more than 400iu OD.
Vitamin K (Menadiol Diphosphate)	10mg OD PO	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Safe in pregnancy. **Lactation** Can use in breast-feeding.

Section 7.3: Gastro-oesophageal reflux

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Esomeprazole (2nd line)	20 – 40mg OD	Dose can be increased to maximum of 160mg daily in divided doses according to response in resistant cases or Zollinger-Ellison Syndrome Maximum single dose is 80mg. Doses greater than 80mg given in 2 divided doses.	**Hepatic effects** Severe hepatic impairment max. 20mg OD. In pts. <40kg with severe hepatic impairment max 10mg OD. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Clinical data on exposed pregnancies are insufficient. Animal studies do not indicate direct or indirect harmful effects with respect to embryo/foetal development. The very limited published data do not suggest an increased risk of congenital malformations or other forms of foetal toxicity associated with the use during pregnancy. However, data is too limited to state that there is no increase in risk. Use with caution in pregnancy if treatment with alternatives which are known to be safe (such as omeprazole or ranitidine) cannot be used. **Lactation** It is not known whether esomeprazole is excreted in human breast milk. No studies in lactating women have been performed; therefore the manufacturer suggests that esomeprazole should not be used during breast-feeding. There have been, however, no reports found regarding neonatal toxicity following exposure to esomeprazole during lactation.
Gaviscon® Advance	5-10mL as required after meals & at bedtime	May damage enteric coatings designed to prevent dissolution in the stomach, therefore not to be used at the same time as E.C. preparations 10ml contains 4.6mmol Na^+ & 2mmol of K^+. This should be taken in to account in patients on a salt restricted diet.	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Safe in pregnancy. **Lactation** Can be used during breast-feeding.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Lansoprazole (1st line)	15-30mg OD	Dose can be increased to max. 180mg daily according to response in resistant cases or Zollinger-Ellison Syndrome. Daily doses > 120mg given in 2 divided doses. FasTab tablet should be placed on the tongue & gently sucked. FasTab can also be dissolved in water & administered down NG tube or oral syringe.	**Hepatic effects** In pts with moderate or severe liver disease LFTs must be monitored regularly & max daily dose of 15-30mg given. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Manufacturer advises avoid in pregnancy. Animal studies do not reveal any teratogenic effects, however, reproduction studies indicate slightly reduced litter survival and weights in rats and rabbits given very high doses of lansoprazole. Whilst limited published data do not suggest an increased risk of congenital malformations or other forms of foetal toxicity. However, data is too limited to state that there is no increase in risk. **Lactation** Avoid: there is no information on the secretion of lansoprazole into breast milk in humans.
Omeprazole (1st line)	20- 40mg daily 40mg OD IV (short term use only when oral route not possible)	Oral dose can be increased to 120mg daily according to response in resistant cases or Zollinger-Ellison Syndrome Max. single dose 80mg. Doses greater than 80mg given in 2 divided doses. IV administration: By slow IV bolus or IV infusion in 100ml N/S 0.9% or Glucose 5% over 15-30mins, depending on preparation & brand. Please check manufacturer's instruction or contact pharmacy for advice. MUPS/Dispersible tablets: Can be dispersed in water. Enteric coated pellets must not be chewed.	**Hepatic effects** In pts with hepatic impairment max daily oral & IV dose is 20mg. Monitor LFTs. If LFTs rise discontinue treatment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Results from three prospective epidemiological studies (more than 1000 exposed outcomes) indicate no adverse effects of omeprazole on pregnancy or on the health of the foetus/newborn child. Omeprazole can be used during pregnancy. **Lactation** Omeprazole is excreted in breast milk but is not likely to influence the child when therapeutic doses are used. Can be used in breastfeeding.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Pantoprazole (3rd line)	20-40mg OD 40mg OD IV (short term use only when oral route not possible)	Oral dose can be increased to max. 160mg daily according to response in resistant cases or Zollinger-Ellison Syndrome Max. single dose 80mg. Doses greater than 80mg given in 2 divided doses. IV administration: By slow IV bolus or IV infusion in 100ml N/S 0.9% or Glucose 5% over 15-30mins.	**Hepatic effects** In severe hepatic impairment max. daily oral & IV dose is 20mg. Monitor LFTs. If LFTs rise discontinue treatment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** There are no adequate data from the use of pantoprazole in pregnant women. Studies in animals have shown reproductive toxicity, therefore avoid in pregnancy. **Lactation** Animal studies have shown excretion in breast milk & excretion into human milk reported. Do not use in breast-feeding.
Ranitidine	150mg BD or 300mg ON	Oral dose can be increased to max. 300mg BD according to response in severe cases As per our practice at RBH – may be prescribed with PPI if needed as adjunct therapy.	**Hepatic effects** No dose change in hepatic impairment. **Renal Impairment** **GFR 20-50Ml/min** dose as in normal renal function **GFR 10-20Ml/min** dose as in normal renal function **GFR <10Ml/min** 50-100% of normal dose.	**Pregnancy** Can be used in pregnancy. Documented experience in approximately 1500 exposed pregnancies. One study showed no increased risk of major malformations after 1st trimester exposure. Other studies also argue against a teratogenic potential in humans. Considerable experience in late pregnancy, with no adverse neonatal effects attributed to ranitidine. Published data do not indicate that use of ranitidine is associated with an increased risk of congenital malformations or other adverse fetal effects. **Lactation** It is excreted in breast milk. Maternal ranitidine not expected to cause any adverse effects in breastfed infants. There were no reports found regarding neonatal toxicity following exposure to ranitidine during lactation.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Sucralfate (aluminium sucrose sulphate)	2g BD OM & ON PO or 1g QDS po1 hour before meals & at bedtime.	Maximum dose: 8g/day Avoid in patients receiving enteral feed or delayed gastric emptying due to risk of bezoar formation.	**Hepatic effects** No dose adjustment in hepatic impairment **Renal Impairment** **GFR 20-50mL/min** 4g daily **GFR 10-20mL/min** 2-4g daily **GFR <10mL/min** 2-4g daily	**Pregnancy** Absorption from GI tract negligible. Teratogenicity studies in mice, rats and rabbits at doses up to 50 times the human dose have revealed no evidence of harm to the foetus. Can be used in pregnancy. Lactation Minimal if any excretion in breast milk.

Section 7.4: Antiemetics

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Domperidone	10mg TDS PO (usual max 10mg TDS – increased doses may increase risk of cardiac adverse events).	Rare side effects include galactorrhoea, gynaecomastia, amenorrhoea and hyperprolactinaemia.	**Hepatic effects** Despite manufacturers contraindicating its use, domperidone is the drug of choice in many liver centres as it has minimal side effects and can be used in all liver patients at usual starting dose 10mg TDS. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** There are limited post-marketing data on the use of domperidone in pregnant women. A study in rats has shown reproductive toxicity at a high, maternally toxic dose. The potential risk for humans is unknown. Therefore avoid in pregnancy. **Lactation** It is excreted in breast milk of lactating rats. Concentrations in breast milk of lactating women are 10 to 50% of the corresponding plasma concentrations. It is not known whether this is harmful to the newborn. Breast-feeding is not recommended.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Levomepromazine	3mg-6mg or 3.125mg - 6.25mg ON PO or SC. Can be increased to 12.5mg -25mg BD according to response	Warn patients of pronounced sedative effects – may be negated by starting with small doses and titrating. Use higher doses at night if necessary.	**Hepatic effects** Avoid in hepatic impairment. **Renal Impairment** **GFR 20-50mL/min** dose as in normal renal function **GFR 10-20mL/min** dose as in normal renal function **GFR <10mL/min** start with small dose & increase as necessary.	**Pregnancy** Not recommended in pregnancy. **Lactation** Not recommended in breast-feeding.
Metoclopramide	10mg 8 hourly Po or IV bolus <40 kg: 5mg 8 hourly Po or IV bolus	Should be avoided in patients under 20yrs due to increased risk of extrapyramidal reactions involving facial and skeletal muscle spasms and oculogyric crises. Avoid in patients with epilepsy as frequency and severity of seizures may be increased. Use with caution after discussion with consultant due to risk of extrapyramidal side effects.	**Hepatic effects** Avoid in moderate to severe hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** No adverse foetal effects were reported in studies during 1st & 2nd trimester, with no significant risk of major malformations. No adverse birth outcomes in study of 309 women exposed in 1st trimester. Has been used in all stages of pregnancy, no evidence of embryo, foetal, or newborn harm found in human and animal studies, so can be used. **Lactation** Metoclopramide is secreted into breast milk. Effects on newborn cannot be excluded. Adverse effects reported in 2 infants (mild intestinal discomfort), therefore avoid in breast-feeding.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ondansetron	4-8mg 8 hourly PO or IV bolus <40kg: 4mg 8 hourly PO or IV bolus	In patients. > 40kg additional PRN dosing may be given up to total maximum daily dose of 32mg.	**Hepatic effects** In patients with moderate to severe hepatic impairment the maximum daily dose is 8mg i.e 4mg 12 hourly. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Safety of ondansetron in human pregnancy has not been established. Experimental animal studies do not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and pre- and post-natal development. However, not recommended by manufacturer. Limited human data & animal reproductive studies show low risk of malformation. Where other anti-emetics have failed use of ondansetron may be considered. Has been used in pregnancy with no harmful effects. **Lactation** No reports on use in human lactation. Shown to pass into the milk of lactating animals, therefore not recommended in breast-feeding.

Section 7.5: Treatment of constipation and Distal Intestinal Obstruction Sydrome (DIOS)

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Acetylcysteine 20% injection (oral & rectal)	Po: 30mL TDS in 150mL orange juice or water PR: 30mL added to phosphate enema TDS	Monitor electrolytes daily Acetylcyetine 20% Injection preparation used for PO/PR administration	**Hepatic effects** No dose change in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** It is not teratogenic or embryotoxic in experimental animals, although data is limited, does not appear to represent a risk to the foetus when given IV for paracetamol overdose. No reported pregnancy data on its use as a mucolytic. **Lactation** No reports in breastfeeding, although IV acetylcysteine has been administered to pre-term neonates at greater doses than would be obtained in breast milk without causing toxicity. Best to avoid breast-feeding.
Gastrografin® (oral & rectal)	50-100mL OD PO/PR with 200-400mL water	Due to Gastrografin® being very hypertonic patients must be well hydrated and advised to drink plenty of fluids. Where patients cannot take fluids orally then IV fluids should be given	**Hepatic effects** No information available on dose adjustments in hepatic impairment. Use with caution & monitor LFTs. **Renal Impairment** No information available on dose adjustments in renal impairment. Use with caution & monitor renal function as increased risk of worsening renal impairment.	**Pregnancy** Adequate and well-controlled studies in pregnant women have not been conducted. Animal studies do not indicate direct or indirect harmful effects with respect to embryo / foetal development. Caution should be exercised when using Gastrografin in pregnant women. **Lactation** Not known if excreted in breast milk, therefore avoid.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Klean-prep	Up to 4 sachets a day	Monitor electrolytes daily Do not give at bedtime due to risk of aspiration. Dissolve each sachet in 1 litre of water and drink within 1 hour. (The contents of all 4 sachets should be taken within 4-6 hours) If given via NG tube usual rate 20-30mL/min	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** Should only be used during pregnancy if considered essential by the physician. There is no experience of use during pregnancy. Not absorbed from gut, no teratogenic effects reported in pre-clinical studies, although no published studies on potential teratogenicity in human pregnancy. **Lactation** Avoid in breast-feeding.
Lactulose	15-20mL BD PO	Adjust dose according to response	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function.	**Pregnancy** Can be used in pregnancy. **Lactation** Can be used during breast-feeding.
Movicol®	1-3 sachets daily in divided doses PO	Monitor electrolytes May be increased to 8 sachets/day in divided doses Dissolve each sachet in 125ml water No more than 2 sachets should be taken in 1 hour.	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function	**Pregnancy** There are no or limited data from use in pregnant women. Studies in animals have shown reproductive toxicity. Indirect embryofoetal effects noted in rabbits. Not absorbed from gut, no teratogenic effects reported in pre-clinical studies, although no published studies on potential teratogenicity in human pregnancy, therefore only use if benefit outweighs risk. **Lactation** Can be used in breastfeeding.

Section 8 Bone Health

Section 8.1 Oral agents

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Alendronic acid (1st line)	70mg once a week PO	Due to risk of osteonecrosis of the jaw patients should maintain good oral hygiene, have routine dental checks & report any oral symptoms. Patients should be advised to report any thigh, hip or groin pain during treatment. Tablet must be taken at least 30 minutes before breakfast, any other drinks other than plain water & other medicines. Swallow whole with a full glass of water & sit or remain upright for at least 30minutes after taking. Counsel young women with respect to planning future pregnancies.	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **GFR 35-50mL/min** Dose as in normal renal function **GFR <35mL/min** Avoid	**Pregnancy** Do not use in pregnancy: no adequate data from use in pregnant women. Alendronic acid given during pregnancy in rats caused dystocia related to hypocalcaemia. **Lactation** Do not use in breastfeeding. It is not known whether it is excreted into human breast milk.

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Calcium and Vitamin D Preparations	Adcal-D3 (Chewable & Effervescent tablets) 1 tablet BD	Calcium 600mg (15mmol), colecalciferol 400 units (10mcg)/tablet Effervescent tablets should be dissolved in 200mL of water	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **GFR 10-50 mL/min** Use with caution. **GFR<10mL/min** Avoid In patients with renal impairment monitor plasma phosphate, Ca^{+2} levels & urinary Ca^{+2} excretion & titrate dose according to plasma levels In patients with severe renal insufficiency, colecalciferol is not metabolised in the normal way and alternative forms of vitamin D must be used.	**Pregnancy** Vitamin D deficiency has been associated with maternal & foetal complications such as pre-eclampsia, gestational diabetes, increase incidence of pre-term delivery, stillbirth and poor foetal bone development & growth retardation. Can use in pregnancy but maternal plasma calcium levels must be monitored. **Lactation** Vitamin D and its metabolites pass into the breast milk. Can be used in breastfeeding but monitor plasma calcium levels.
	Cacit D3 Granules 1-2 sachets daily	Calcium 500mg (12.5mmol), colecalciferol 440 units (11mcg)/tablet Dissolve sachet in large glass of water		
	Calceos Chewable tablets 1 tablet BD	Calcium 500mg (12.5mmol), colecalciferol 400 units (10mcg)/tablet		
	Calcichew D3 1 tablet BD - TDS	Calcium 500mg (12.5mmol), colecalciferol 200 units (5mcg)/tablet Chew or suck tablet		
	Calcichew D3 Forte/Calcichew D3 Caplet 1 tablet BD	Calcium 500mg (12.5mmol), colecalciferol 400 units (10mcg)/tablet Caplets may be swallowed – Forte tablets suck/chew		

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Risedronate (2nd line)	35mg once a week PO	As for alendronate (see notes above)	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **GFR >20mL/min**: Dose as in normal renal function **GFR < 20mL/min:** Avoid	**Pregnancy** No adequate data from use in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Do not use in pregnancy. **Lactation** Do not use in breast-feeding Studies in animals indicate that a small amount of risedronate sodium pass into breast milk.
Strontium Ranelate (sachet)	2g OD PO	Life-threatening cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms have been reported. Patients should be advised of the signs and symptoms & monitored closely for skin reactions. The highest risk for occurrence is within the first weeks of treatment (3-6 weeks) Absorption reduced by food & milk, therefore avoid food for 2 hours after taking Dissolve sachet in at least 30mL water.	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **GFR >30mL/min:** Dose as in normal renal function **GFR <30 mL/min**: Avoid.	**Pregnancy** Do not use in pregnancy. **Lactation** Do not use in breast-feeding. Expected to cross in to breast milk.

Section 8.2 Other agents

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ibandronic acid injection	3mg every 3 months	Use when oral treatment not tolerated or effective or on advice of consultant endocrinologist. Administer by slow IV bolus. If dose is missed should be given asap & 3 monthly thereafter. Due to risk of osteonecrosis of the jaw patients. should maintain good oral hygiene, have routine dental checks & report any oral symptoms. Patients should be advised to report any thigh, hip or groin pain during treatment. Counsel young women with respect to planning future pregnancies.	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **GFR >30mL/min:** Dose as in normal renal function **GFR < 30mL/min.** Avoid	**Pregnancy** Do not use in pregnancy. No reports on use in pregnancy. Animal studies showed reproductive toxicity. Theoretical risk of harm to foetus e.g. skeletal and other abnormalities. **Lactation** Do not use in breast-feeding. No reports of ibandronic acid use in breastfeeding.
Teriparatide (Last line on consultant endocrinologist decision only)	20mcg OD SC injection	Inject by SC injection in thigh or abdomen Maximum duration of treatment is 24 months	**Hepatic effects** Use with caution in hepatic impairment. **Renal Impairment** Use with caution in moderate renal impairment. Avoid in severe renal impairment.	**Pregnancy** Do not use in pregnancy. Studies in rabbits have shown reproductive toxicity. Effect on human foetal development has not been studied. Potential risk for humans is unknown. **Lactation** Do not use in breast-feeding. Not known whether excreted in human milk.

Section 9 Haemoptysis

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Terlipressin	Initially 2mg then 1-2mg every 4-6 hours until bleeding is controlled, (maximum duration 72 hours).	As terlipressin has antidiuretic and pressor activity it should be used with great caution in patients with hypertension, atherosclerosis, cardiac dysrhythmias or coronary insufficiency. Constant monitoring of blood pressure, serum sodium and potassium and fluid balance is essential.	**Hepatic Impairment** A dose adjustment is not required in patients with liver failure. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function. Use with caution. **GFR <10mL/min** Dose as in normal renal function. Use with caution.	**Pregnancy** Not recommended by manufacturer, however, benefit may outweigh risk in clinical situation where this is required. **Lactation** No information available. Manufacturer advises avoid.
Tranexamic Acid	PO: 500mg – 1g every 8 hours IV: 500mg – 1g every 8 hours[viii]		**Hepatic Impairment** No specific dose reduction recommended. **Renal Impairment** **GFR 20-50mL/min** IV: 10mg/kg 12 hourly. Oral: 25mg/kg 12 hourly **GFR 10-20mL/min** IV: 10mg/kg 12-24 hourly. Oral: 25mg/kg 12-24 hourly. **GFR <10mL/min** IV: 5mg/kg 12-24 hourly. Oral: 12.5mg/kg 12-24 hourly	**Pregnancy** No adverse effects attributed to use during pregnancy in humans. Limited amount of data available at present does not support an association between the use of tranexamic acid during pregnancy and an increased risk of venous thrombosis. If use of tranexamic acid is indicated in the treatment of maternal illness treatment should not be withheld on account of pregnancy. **Lactation** Tranexamic acid passes into breast milk - an antifibrinolytic effect in the infant is unlikely.

Section 10 CF Related Liver Disease

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Ursodeoxycholic Acid	20mg/kg/day in 2 – 3 divided doses[ix] (we usually dose BD). The dose may need to be increased gradually to target dose to avoid adverse effects.	Improvement of hepatic metabolism of essential fatty acids and bile flow	**Hepatic effects** No dose adjustment in hepatic impairment. **Renal Impairment** **(all levels)** Dose as in normal renal function.	**Pregnancy** Animal studies have not shown direct teratogenic effects when administered to pregnant rats, mice & rabbits. Use in treatment of intrahepatic cholestatsis of pregnancy appears to be low risk for the foetus. Data in 1st trimester is extremely limited & lacking, although the limited data available has not shown an increased risk of congenital malformations. Use in later pregnancy 2nd & 3rd trimester have not shown any adverse foetal outcome. Only use if benefit outweighs the risk. **Lactation** No reports of use during lactation. Avoid in brest-feeding.

Section 11 Immunomodulators

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy & Lactation
Azithromycin	< 40 kg: 250 mg three times a week > 40 kg: 500 mg three times a week *Usually Monday, Wednesday and Friday* Alternative dose: 250 mg OD to aid adherence or to reduce GI side effects; Dose can be increased to 500mg OD if deterioration, on **consultant's decision**	Long-term benefits independent of microbiology: for immuno-modulatory effect. Patients should be advised to stop azithromycin treatment and seek advice if they experience any changes in their hearing such as tinnitus. Avoid single agent treatment with a macrolide in patients who have grown *M. abscessus* or *M. avium* due to risk of emergent resistance with unopposed macrolides. Patients prescribed long term azithromycin should have baseline ECG to identify QTc prolongation. Use with caution if QTc prolonged. Repeat at annual review.	**Hepatic effects** Check liver function 1 month after commencing continuous azithromycin therapy. No dose adjustments are needed in mild to moderate liver impairment; monitor LFTs. Avoid in severe liver disease. **Renal Impairment** **GFR 20-50mL/min** Dose as in normal renal function **GFR 10-20mL/min** Dose as in normal renal function **GFR <10mL/min** Caution due to 33% increase in systemic exposure to azithromycin.	**Pregnancy** Not associated with an increased risk of malformations or adverse pregnancy outcome. **Lactation** Because of the low levels of azithromycin in breast milk and use in infants in higher doses, it would not be expected to cause adverse effects in breastfed infants. Monitor for possible effects on the gastrointestinal flora, such as diarrhoea, candidiasis.

Section 12 CFTR Modifying Drugs

Drug	Dose	Additional Information, Counselling and Monitoring, Administration	Liver/Renal considerations	Pregnancy and Lactation
Ivacaftor	Patients with confirmed G551D CFTR mutation: 150mg BD	All patients must have had a sweat chloride test within the 6 months prior to starting treatment and be informed of the stopping criteria at the time of starting treatment with ivacaftor (see specialised commissioning policy: 'Ivacaftor for Cystic Fibrosis.') Refer to **RBH 'Guidelines for the use of ivacaftor in adult and paediatric patients with cystic fibrosis.**' Ivacaftor should be taken with a fat-containing meal. Liver function tests are recommended prior to initiating ivacaftor, every 3 months during the first year of treatment, and annually thereafter. When co-administered with potent inhibitors of cytochrome p450 isoenzyme CYP3A (such as itraconazole, posaconazole, voriconazole, clarithromycin), reduce dose of ivacaftor to 150mg twice weekly. When co-administered with moderate inhibitors of CYP3A (such as fluconazole, erythromycin), reduce dose of ivacaftor to 150mg once daily.	**Hepatic effects** Mild hepatic impairment (**Child-Pugh A**): No dose adjustment necessary. Moderate hepatic impairment (**Child-Pugh B**): Reduce dose to 150mg once daily Severe impairment (**Child-Pugh C**): No clinical experience – if benefits outweigh risk consider starting dose 150mg once daily on alternate days and adjust according to response and toleratbility. **Renal Impairment** **GFR >30mL/min** No dose adjustment necessary. **GFR ≤30mL/min** Negligible urinary excretion, however, manufacturer advises caution: adjust dose if necessary according to response/tolerability.	**Pregnancy** No information available in human pregnancy. Developmental toxicity studies have been performed in rats and rabbits at daily doses up to 5 times the human daily dose and have revealed no evidence of harm to the foetus due to ivacaftor. Because animal reproduction studies are not always predictive of human response, Kalydeco should be used during pregnancy only if clearly needed. **Lactation** The safe use of ivacaftor during breast-feeding has not been established: it is unknown whether ivacaftor and/or its metabolites are excreted in human milk. Ivacaftor was shown to be excreted into the milk of lactating female rats; however, in humans, ivacaftor is highly protein bound (99%). Drugs that are highly protein bound are less likely to pass from the bloodstream into breast milk. Continue if potential benefits outweigh any potential risks.