Title	Renal complications
Version	1.0

1. Introduction

- Kidney disease is becoming more common for the patient with CF.
- The CFTR protein is expressed throughout the whole of the nephron so it is not surprising that there is growing recognition of the effects of CF on the kidney.
- Drug excretion by the kidney, their ability to concentrate and dilute the urine and the ability to excrete a salt load are all altered in CF.
- Pathology in CF does not seem to result from primary renal disease but rather as secondary renal dysfunction from both the complications of the CF and the treatments used in its management.
- Therefore, as the age of the CF population increases there is an increasing risk of acute kidney injury, chronic renal failure and the potential need for dialysis and kidney transplantation.

2. Drug nephrotoxicity: notable drugs

- Anti-Pseudomonal/IV antibiotics: aminoglycoside and colistin
- Immunosuppressive treatments such as cyclosporine and tacrolimus used post-transplant
- Some other commonly used antibiotics and others can potentially cause renal damage:
  - ciprofloxacin, rifampicin, azithromycin, ceftazidime
- Anti-tuberculous (Mycobacteria Abscessus) drugs: amikacin
- anti-inflammatory drugs such as NSAIDS

3. Aminoglycosides

3.1. Toxicity

3.1.1. Aminoglycosides are directly toxic to the proximal renal tubules of the kidney and their effect is relative to a person's total cumulative lifetime dose and correlates directly with a reduction in GFR. Co-administration of colomycin potentiates this effect.

3.1.2. In addition, aminoglycosides are also commonly implicated in cases of acute renal failure. This is complicated by the enhanced renal clearance of aminoglycosides (and penicillins) in CF meaning the achievement of high concentrations are required for bactericidal effect.

3.2. Tobramycin: the least nephrotoxic of the aminoglycosides is the recognised preferred intravenous aminoglycoside for most gram-negative bacteria such has pseudomonas.

3.2.1. **Once daily dosing of tobramycin**

Reducing the dosing interval to once daily dosing allows reduced the accumulation of the drug in the kidney whilst still allowing a high peak concentration and a post antibiotic effect of bactericidal killing (continued bacterial killing when the drug has become undetectable.

3.2.2. **Serum tobramycin levels**

Close monitoring required, as recommended by local Microbiology Services, by:

a) a trough level of less than 1mg/L acceptable. The first level is taken 24 hours after the first dose (just before the second dose) and weekly thereafter, or

b) post-dose level taken 6-14 hours after 1st and 8th dose (or sooner if abnormal levels or clinical concern) and interpreted by the Hartford nomogram.

3.3. Inhaled versus intravenous therapy

- A strategy now widely used to reduce nephrotoxicity is the use of an inhaled aminoglycoside as part of an acute intravenous antibiotic regime. This allows for high levels of lung deposition with low systemic levels reducing side effects including kidney toxicity.
- Caution is required however as even inhaled antibiotics have been shown to reach significant serum levels (albeit lower than with intravenous preparations) and there are reports of renal failure with both nebulised colistin and tobramycin.

3.4. Reno-protection drugs

- Drugs that compete for the renal binding site of aminoglycoside may also be used to reduce nephrotoxicity. The antibiotic fosfomycin is one such option under review
- Statins are currently being investigated for their renoprotective effects against aminoglycosides in CF.

3.5. Instructions for patients on IV aminoglycoside treatment

Patients/Parents/carers to be aware of the need for:

- Renal function test at start of course (or very recently measures)
- Aminoglycoside blood/serum levels, taken as above
- CF Team must be immediately informed, and further IV doses with-held, if patient develops vomiting, diarrhoea or lack of fluid intake for any reason

4. Immunosuppressive Drugs

- As the number of post lung and liver transplant survivors increases the rate of transplant related complications will also increase. Cyclosporine and Tacrolimus (Calcineurin inhibitors) used in the maintenance of immunosuppression reduce glomerular and hence renal blood flow. This in time leads to reduced GFR and progressive kidney damage and potentially to renal failure. This process is compounded in those with CFRD and its renal complications.
- Slowing kidney disease post-transplant can be challenging. Approaches such as targeting a lower blood level or using newer maintenance therapies such as Sirolimus may be trialled, but without their own complications.
- All patients with a change in kidney function should have close monitoring of their immunosuppression and even closer liaison with their transplantation team.
- Checking of immunosuppressive drug levels will likely be required but should be undertaken on the advice of the transplantation team as should any changes to their immunosuppressive therapy.

5. Monitoring of renal function

In practice the measurement of renal function in the clinical setting remains crude. We presently rely on the measurement of eGFR (cockroft gault / aMDRD) as an estimate of kidney function. We must remain aware that this measure is insensitive in detecting early kidney damage with a loss of 30% of nephrons before GFR alters. In addition, it is not validated in the CF population who often have low muscle mass and an increased metabolic state which will influence creatinine production and likely over-estimate creatinine clearance and underestimate renal impairment. However, at present there is no more accurate clinically available alternative.

5.1. Requirements:

- eGFR should be measured for all patients at annual review, during any acute illness, and in adults at the beginning, during and end of intravenous antibiotic therapy.
- In the acute setting use of intravenous aminoglycosides are associated with hypokalaemia, hypomagnesaemia and hypocalcaemia and so these electrolytes as well as renal function require weekly monitoring whilst on IV antibiotic therapy.
- Classification of renal dysfunction in adults is as per the Kidney disease: improving global outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease (reference 4)
- Protein loss from the kidney should be measured as part of assessment of kidney disease secondary to CFRD.
- All patients with an eGFR <90 should have their urine dipped for protein and sent for urine albumin creatinine ratio.
- All PWCF with an eGFR below 90/60 should be referred for assessment by a renal physician.

5.2. Future advances

Enzymes released by the nephron during periods of damage have been studied for many years as a biomarker of renal damage but as yet are not available for clinical use. Biomarkers such as NGAL (neutrophil gelatinase associated lipocalin) and KIM-1 (kidney injury molecule 1) have all shown promise as indicators of acute kidney injury and further studies are awaited.

6. Renal disease related to CF-related Diabetes

- Management of renal disease in the context of CFRD is the same as for a person without CF.
- Evidence of renal disease as measured by eGFR or proteinuria (measured annually with an albumin/creatinine ratio) would lead to the aim of optimizing glycaemic control as well as blood pressure control to maintain BP below 140/80.
- Screening for other complications should have also taken place. Please see section on CFRD for further information

7. Kidney stones in CF

7.1. Risk and mechanisms

- CF provides the ideal conditions for renal stone formation and occurs in up to 6% of the CF population.
- Dehydration, salt depletion and low urine volumes all lead to potentially high levels of oxalate, urate and calcium in the urine. High urate in the urine can lead to calcium oxalate stone formation and has previously been associated with high doses of pancreatic enzymes.
- Frequent and repeated courses of antibiotics lead to the depletion of *Oxalobacter formigenes* in the intestine, which degrades gut oxalates, and in their absence there is increased absorption of gut oxalate.
- In addition, in the presence of malabsorption calcium will bind to excess fatty acids in preference to free oxalate leading to further increased absorption of oxalates. This is further exacerbated by malabsorption of bile acids.
- Citrates are known to be inhibitors of stone formation by reducing the amount of available calcium in the urine.

7.2. Kidney stone management

- Increasing fluid intake, supplementing potassium citrate, reducing foods rich in oxalate (spinach and chocolate) and supplementing low dietary calcium are some of the conservative measures that can be taken to reduce stone formation.
- Supplementing oral oxalate degrading bacteria such as with the use of probiotics may be of some benefit.
- Investigations include renal ultrasound, intravenous pyelogram or helical CT.
- Definitive treatment options include lithotripsy ureteroscopy with stone extraction and ureteric stenting. In some obstructive cases ureteral stents and or the use of percutaneous nephrostomies may be necessary.

8. Other Kidney Diseases Reported in CF

8.1. IgA nephropathy

IgA nephropathy is the most reported glomerulonephritis in CF. In chronic infection and inflammation circulating levels of IgA are high and deposit in the kidneys causing glomerulonephritis.

8.2. Amyloidosis

The continued cycle of chronic infection and inflammation can result in the development of secondary amyloidosis. This thankfully remains a rare complication as it carries a poor prognosis. It typically presents with blood and protein in the urine with an associated declining renal function.

9. Pseudo-Bartters Syndrome

- **Description**
  - An uncommon cause of metabolic alkalosis, sometimes a as a presenting feature of CF as well as a complication in those with known disease.
  - It is accompanied by chronic salt depletion and sometimes faltering growth without severe dehydration.
  - Principal findings are hypokalaemic, hypochloraemic metabolic alkalosis, sometimes with hyponatraemia

- **Presentation**
  - May present acutely often as part of heat stroke in hot weather when there has been inadequate salt and fluid replacement with dehydration.
  - May be preceded by anorexia, nausea, vomiting, fever and weight loss, and in the acute setting can be mistaken for infective gastroenteritis.
  - Judging degree of dehydration in an acute presentation can be hard, the classic clinical signs of dehydration (sunken eyes, loss of skin turgor) not always apparent and a comparison of acute presentation weight with last clinic weight is helpful.
- **Investigation**
  - Venous bicarbonate, chloride, U&Es, creatinine
  - Urinary sodium
- **Management**
  - Acutely oral rehydration solution (Dioralyte or equivalent) or sometimes IV fluids (0.9% sodium chloride +/- potassium chloride) is required.
  - In the more chronic, indolent presentation treatment is with sodium +/- potassium chloride supplements, which may be required for many months or long term.
  - After salt replacement, the metabolic abnormality resolves, and weight gain follows rapidly.

10. References

1. cfmedicine.org Nazareth D, Walshaw M. A review of renal disease in cystic fibrosis. Journal of Cystic Fibrosis. 2013 Jul 1;12(4):309-17.
2. Bush A, Bilton D, Hodson M, editors. Hodson and Geddes' Cystic Fibrosis. CRC Press; 2015 Jul 24.
3. Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Levin A, Stevens PE, Bilous RW, Lamb EJ, Coresh J, Levey AS. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(1):5-14.
4. Kidney disease: improving global outcomes (KDIGO) 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1-50

Classification of chronic kidney disease using GFR and ACR categories

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/1.73m²), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk

Increasing risk

[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150